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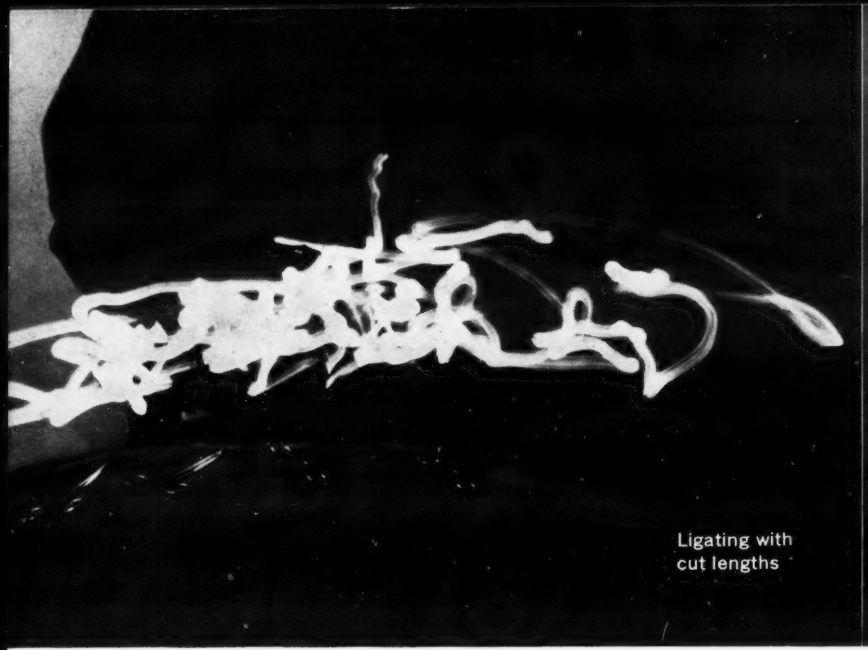

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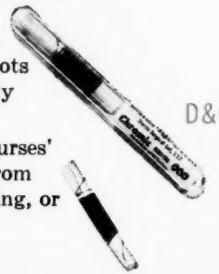

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AN EVALUATION OF PERIPHERAL ARTERIOSCLEROTIC INSUFFICIENCY UTILIZING RADIOACTIVE IODINATED HUMAN SERUM ALBUMIN

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THE USE OF TRACER AMOUNTS of radioactive substances to study the peripheral circulation has introduced a method of study which gives promise of having both objective and quantitative aspects. Since repeated tracer doses can be used with safety, it is possible not only to study the peripheral circulation at the onset, but to evaluate the effect of various therapeutic measures on the status of the circulation. Under certain conditions, prognosis can also be estimated, which may be important for treatment.

The early studies were done with radioactive diffusible ions, sodium by Smith and Quimby and phosphorus by Friedell and associates. Radioactive sodium was also used by Elkin and associates to study the rate of disappearance from an injected site in muscle as an indirect method of studying circulation. Although these studies laid the groundwork for this method, the diffusibility of the ions led to certain uncontrollable variables and problems which detracted from their usefulness. Red blood cells tagged with radioactive phosphorus by Hevesy or radioactive iron by Gibson were used to study circulation, and although this method seems to overcome the problem of diffusibility, it introduced other problems, namely irregular distribution of tagged red blood cells and the susceptibility of these blood cells to destruction.

The use of radioactive iodinated human serum albumin apparently decreased the problem of distribution and diffusibility and according to Krieger improved the ease of handling. The placing of substances within the vascular tree, which remain there for the period of study, has obviously many advantages. If the geometric setup and counting method could accurately measure the rate of blood flow or volume of blood or both through an organ or extremity, the technique would become extremely valuable.

METHOD

This study has been confined to the lower extremity.

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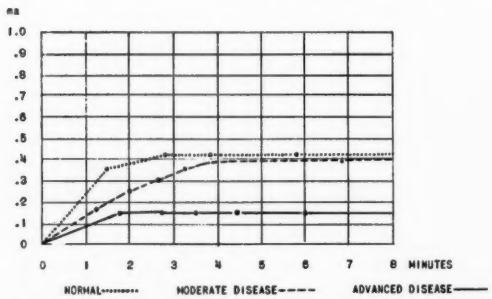

FIG. 1. Build-up curve of circulation using radioactive iodinated human serum albumin.

The patient is placed in the recumbent position with a pillow under the head. No attempt was made to maintain a constant temperature, but the room was quiet, restful, and free from drafts. The face of the lead shielded scintillation counter is placed in contact with the medial malleolus. Forty microcuries of radioactive iodinated human serum albumin, 1 cubic centimeter in volume, are injected into an antecubital vein. When the injection is completed, the counts per minute, recorded graphically by an Esterline Angus plus count rate meter apparatus, show a gradual increase to a point where they become more or less constant, the so-called plateau (Fig. 1). This period of time from the initial increase in counts per minute above background to constant level or plateau is termed the time of equilibrium and from this is derived the circulation index as described by Krieger and associates.

TABLE I.—GROUPING ON BASIS OF CLINICAL AND RADIOLOGIC FINDINGS

	R.I.H.S.A. circulation		
Clinical findings	*Foot to femoral per cent*	*Calf to femoral, per cent*	*Thigh to femoral, per cent*
Group I			
No evidence of vascular disease	14	23	42
Group II			
Atrophy of skin Nails ridged Loss of hair Intermittent claudications	19	28	50
Group IIIa			
Above findings Solitary uninfected ulcer	23	30	54
AFFECTED LEG			
Group IIIb			
Above findings Marked infection	26	33	45
Group IVa			
Above findings Muscle atrophy Rest pain Dry gangrene of one or more toes	18	25	40
Group IVb			
Evidence of massive occlusion with line of demarcation below the knee	11	20	44

After equilibrium is established, the number of counts are determined for 1 minute periods. Counts are taken over the ankle, calf, and thigh and compared to readings taken over the region of the femoral artery near the inguinal ligament. They are converted to percentages by using counts over the region of the femoral artery to 100 per cent. We have found that comparison of ankle counts to femoral counts have been more important and have used this proportion as the ankle to femoral (A/F) ratio. These percentages have been used for comparison of patients because actual counts do not allow for variations in size, body build, and differences of circulation between extremities. For this series, control studies of normal subjects have been the base line for comparison. The isotopic findings of analogous areas in conjunction with the clinical, radiologic, or pathologic findings were used in evaluating the circulatory status of an extremity. It was believed that if, in addition, we could obtain a reliable ratio between various landmarks of the same extremity, this would aid in estimating the status of the circulation of the extremity in more detail. By using this procedure, studies were made on 75 patients who were arranged into 4 groups (Table I) on the basis of the following clinical and radiologic (arteriographic) findings.

Group I.—Relatively normal individuals were among this group, their ages ranged from 26 to 39 years. They had no clinically demonstrable evidence of vascular disease. The arteriograms of these patients were normal (Fig. 2).

Group II.—These patients had clinical evidence of early arterial insufficiency which was characterized by one or more of the following findings: intermittent claudica-

FIG. 2. FIG. 3. FIG. 4. FIG. 5.

FIG. 2. Normal femoral arteriogram.
FIG. 3. Arteriogram showing segmental obliteration.
FIG. 4. Showing more extensive obliteration.
FIG. 5. Obliterated femoral system, sparse collaterals.

tions, trophic changes of the skin, muscle, and nails, loss of hair on the toes and legs, slight blanching on elevation of the foot, and occasional rest pain. The ages of these patients ranged from 35 to 72 years. Oscillometric studies on the majority of these individuals did not consistently show evidence of impaired circulation. In most cases the arteriograms were abnormal showing segmental obliteration or diminished lumen with increased collateral circulation (Fig. 3).

Group IIIa.—The individuals in this group had one or more of the findings already mentioned plus the presence of a solitary, minimally infected ulcer on the toe or heel. The arteriograms were not significantly different from those of group II.

Group IIIb.—These patients presented clinical evidence of markedly infected ulcers on one or more toes with hyperemia and cellulitis of the foot. Early gangrenous changes had developed. The opposite extremity showed evidence of advanced insufficiency without ulceration.

Group IVa.—These patients had clinically advanced disease. In addition to marked atrophy of the muscle, dry gangrene of one or more toes was present. Rest pain was fairly constant. Arteriographic evidence of obstruction to major vessels was present. The peripheral pulses below the femoral artery were obliterated (Fig. 4).

Group IVb.—These patients were admitted with clinical evidence of acute or sub-

TABLE II.—RANGE OF RESULTS

Clinical findings	*A/F ratio, per cent*	*Time of equilibrium, mins.*	*Circulation index*
Normal	14	1–3	2–3
Moderate disease	19	3–8	3–4
Hyperemia	26	8–2	1–2
Advanced disease	18	above 8	4–5
Occlusive disease	11	18 aver.	above 5

The higher the circulation index, the more inefficient the circulation.

acute occlusion of a major vessel in the lower extremity. They had a line of demarcation which appeared 4 to 8 centimeters below the knee, giving the clinical impression of thrombotic occlusion, superimposed on an arteriosclerotic plaque or embolization. Examination revealed the extremity to be cyanotic, mottled, and cold. The opposite extremity showed evidence of advanced insufficiency. Femoral pulses were palpable. Arteriograms showed obliterated fermoal system with sparse collateral development (Fig. 5).

RANGE OF RESULTS IN CLINICAL GROUPS

After the normals were established it was found that the A/F ratio could be increased by 20 to 30 per cent by the presence of cellulitis or induction of spinal anesthesia. It was found that the patients with arteriosclerosis in clinical groups II and IIIa, that is moderate disease, presented a higher A/F ratio than the normals. It was apparent that we were measuring blood flow as well as blood volume as suggested by Krieger and associates. The reason for the higher ratio is stasis or pooling of blood in the extremity.

This finding is presumably secondary to: (1) a diminished pressure gradient, caused by encroachment of atherosclerotic deposits and proliferated intima upon the lumen of the major vessels, (2) diminished elasticity of the larger vascular radicles by calcific infiltration and fibrosis, (3) increased collateral circulation, and (4) tissue anoxia leading to capillary and venule dilation and increased permeability for liquid components of blood and tendency toward sludging of remaining blood elements. In a normal individual only a portion of the total vascular bed is patent at any particular time. The hyperemia due to cellulitis or spinal anesthesia permits us occasionally to see the potentiality of the system. This portion of the system is our reserve or collateral bed. It is composed of the capillaries, arterioles and venular bed of the skin, muscle, and bone. Consideration of the vascular bed must include the physiologic mechanism as well as the anatomic pattern.

In the patient with progressive arteriosclerosis obliterans, this reserve is gradually used up to compensate for the obliterative changes in the arteries and larger arterioles. The clinical manifestation of hair loss on the foot and leg and of early trophic changes of the skin and muscle testify to the insufficiency. The survival of tissue depends upon the speed with which metabolic products are exchanged as well as upon the volumes presented. This is demonstrated by showing that even though the circulation index may be high the equilibrium time may be prolonged and the A/F ratio low. This finding is an excellent example of disassociation of the various factors used to evaluate the circulatory status of the extremity (Table II).

In the advanced state not only are the major vessels occluded but also the reserve has been depleted. Clinically we see the patient with marked muscle atrophy, dry skin, ridged and hooked nails, no hair on the legs, and gangrene of the digits. Thus the total blood volume in the leg is reduced as well as the blood flow. Radioisotopically this condition is demonstrated by the decrease in A/F ratio to below normal levels as well as a decrease in circulation index.

The status of the reserve or collateral is important in determining the therapy to be directed toward the disorder. Occasionally, the surgeon is confronted with cases of occlusive disease which appear hopeless and

TABLE III.—EFFECT OF AGENTS ON CIRCULATION

Material	*Percentage increase*	*Clinical findings present*
Histamine	5–17*	As long as continued
Priscoline®	3–15†	3–4 hours
Papaverine	3–7	0
Illdar®	3–5	0
Sympathectomy	—17–+30	1 to 3 years
Spinal	—4–+30	?
Hyperemia	+24–+30	when present

*Decreased after sympathectomy.
†10 to 15 per cent after sympathectomy.

may require amputation. With this isotopic technique the circulation may be shown to be better than suspected clinically and thus may be amenable to conservative therapy. We have found several cases in which the isotopic method of determining the circulation is more accurate than the clinical method with avoidance of an amputation.

Using this method we have determined the effect of different medications and operative procedures in arteriosclerosis obliterans. Mufson has been using intra-arterial histamine and other investigators have been using priscoline®. Lumbar sympathectomy has been widely used despite early warning that it be avoided for arteriosclerosis.

EFFECTS OF DRUGS AND OTHER THERAPEUTIC MEASURES ON CIRCULATION

After sympathectomy a 10 to 15 per cent increase in the A/F ratio could be measured when priscoline was given intra-arterially. The overall increase using these agents has not been sufficiently high to warrant the continued clinical use. If a difference normally exists between two legs of up to 10 per cent, is the agent or operative procedure justifiable if it cannot increase the circulation by more than 10 per cent? The effect of these agents has been inconsistent, and we have been unable to predict which cases will respond and to what degree (Table III). Lumbar sympathectomy when performed on patients with moderate disease may give clinical improvement, that is to say, increased skin warmth, hyperemia, disappearance of intermittent claudications, and occasionally decreased rest pain. The change using the radioisotope method ranged from −17 to +30 per cent. We have been unable to demonstrate that such improvement is consistently over 15 per cent. Changes in the build-up time have been demonstrable, however (Fig. 6). In persons with moderate disease a small increase may give satisfactory relief of symptoms but its ability to alter the course of the disease is dubious. We have been unable to measure any improvement consistently in patients with advanced disease. The reserve is shown to be depleted and we now believe that there is no rationale for the use of the operative procedure in these cases.

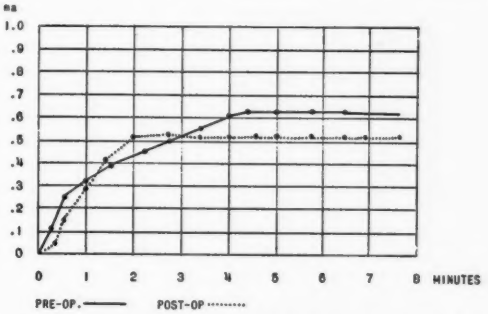

FIG. 6. Build-up curve of circulation before and after sympathectomy.

In patients with an embolic or spastic condition in which marked atrophy is not present, lumbar sympathectomy may produce significant increases in collateral circulation by dilating the reserve system.

CONCLUSIONS

1. This preliminary study confirms the work of Krieger and associates that this method is more accurate than other clinical methods currently available in evaluating the circulation.

2. This method is safe and relatively simple and may be repeated for diagnostic as well as prognostic purposes.

3. The circulation of an extremity may be more efficiently determined by analyzing the circulation index, the build-up curve, and the A/F ratio.

4. It has shown promise as a method of study of the reserve vascular bed and of ways to alter it, such as intra-arterial medications and lumbar sympathectomy.

5. As a result of studies with this method, it is believed that vasodilator drugs may be continued after sympathectomy.

6. The use of sympathectomy in patients with arteriosclerosis obliterans should be limited to those individuals with moderate disease, embolism, and vasospastic conditions.

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LIGATION OF THE INFERIOR VENA CAVA WITH ABSORBABLE GUT

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LIGATION OF THE INFERIOR VENA CAVA to prevent pulmonary embolism has proved valuable in selected cases. While the immediate operative morbidity and mortality of the operation have been low, many patients later have had leg difficulties such as pain, edema, varicosities, and ulceration, alone or in combination. Whether these are chiefly due to postligation venous hypertension or to the effects of preligation or postligation thrombosis of leg veins is not completely clear. Careful management of cooperative patients appears to decrease the leg difficulties significantly in the late postoperative period.

Until recently, attention has centered upon methods of caval ligation which would insure permanency of this venous interruption. Consideration of a patient exhibiting edematous legs following caval ligation led to discussion of the possibility of interrupting venous flow in such a manner that blood flow would later be resumed. Absorbable gut ligation appeared to offer such possibility, and this study was therefore begun in dogs in February 1953.

Several months subsequent to that time, it was learned from W. H. Moretz that he and his associates had had considerable experience with the use of metal clips to occlude the vena cava in dogs. Venograms had shown successful restoration of blood flow following removal of such clips by a pull-out wire. The results of their study have now been published (2). Ten of 12 dogs followed 1½ to 4 months after removal of the clips regained caval patency. Observations of venous pressure, collateral venous pathways, and discussion of fatalities were reported.

In 1953, two other investigative series (1, 7) became available, that of Streuter and Paine being of particular interest since they had evaluated absorbable gut for this purpose in 34 dogs. The results of our laboratory experiences are reported herein, with interpretation of these data and with correlation to these published studies.

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METHODS

Fifty-five mongrel dogs were studied. Operations were performed under nembutal anesthesia and by aseptic technique. The abdomen was opened by a midline or right paramedian incision and the viscera were packed away cephalad. The peritoneum over the vena cava was incised. Further dissection was limited to that necessary to place the ligature in the manner to be described. Packs were then removed and the abdomen closed in layers.

Ligation sites. Four methods of tying the cava were used (Fig. 1): (1) High ligation placed the tie caudad to the renal veins but cephalad to several lumbar veins. This method should allow the lumbar tributary veins to drain blood from the blocked venous system. (2) Low ligation placed the tie caudad to all lumbar veins (including those which entered just at the caval formation by the iliacs), thus decreasing the collateral circulation available to drain blood from the blocked venous system. (3) High plus collateral ligation consisted of the usual high tie plus ligation of all lumbar veins close to the wall of the cava. High caval ligation plus ligation of lumbar veins should

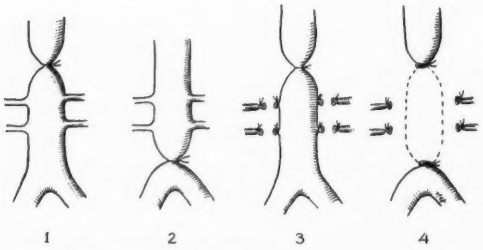


FIG. 1. Sites of ligation of inferior vena cava in dogs.

make the operation similar to a low ligation of the vena cava in that no lumbar veins are left to drain off venous blood. (4) Excision consisted of actual removal of a segment of cava including attached lumbar veins.

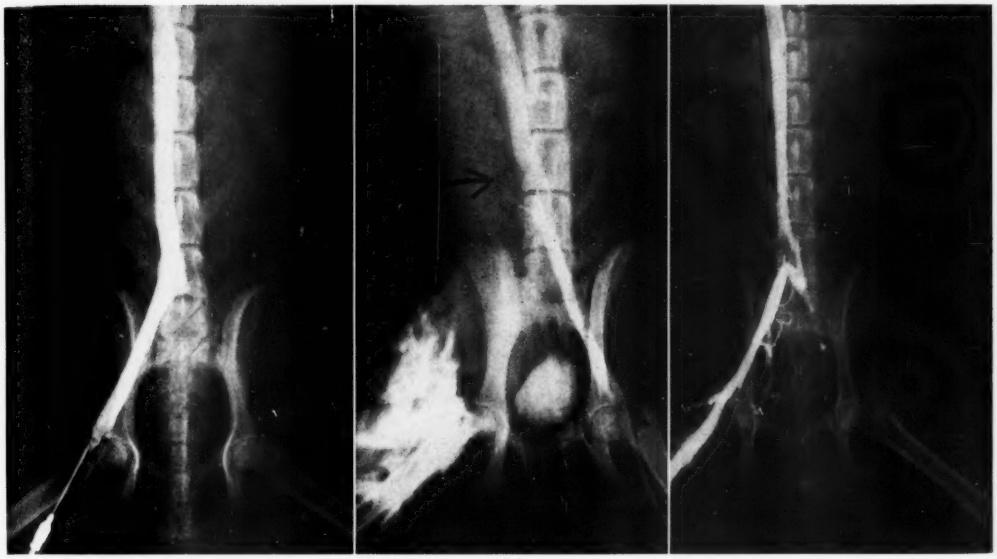
Ligature material. No. 2 chromic gut was used for the first 4 dogs and No. 00 chromic gut for the remainder. Lumbar veins were tied with No. 000 silk (when this was done). In all except 3 dogs the ligature was pulled up snugly and a four throw square knot was placed. In 3 dogs a double loop ligature was placed prior to tying, the method of Streuter and Paine being used. A silver clip was, in each instance, placed on the long ends of the gut to mark the ligation site on x-ray films. The surgical ligation was, in each instance, verified by venograms or autopsy. Figure 2c shows a large direct collateral circumventing the ligature site, illustrating the additional information obtained by venograms.

Venous pressure. Venous pressure determinations were recorded from a saphenous vein before, during, and after operation for several hours, as well as at intervals later. The dog was anesthetized, tied supine upon a table, and the manometer read from the surface of the table. Saline or 5 per cent dextrose was pumped into the manometer and then allowed to flow from it into the vein. The lowest of several repeated determinations was recorded as the venous pressure. In 2 instances, simultaneous venous pressure data were obtained from a needle placed into the right iliac vein through the operative wound. Since both of these indicated the same pressures as the saphenous vein, no further iliac pressures were taken. Experience indicated that venous pressures taken soon after anesthesia induction were abnormally high, and that with time they decreased. This observation has been made in other experiments after injection of nembutal, when venous pressures are always elevated temporarily.

Venograms. Venograms were made 152 times. Initially an infusion of 5 per cent dextrose was connected to a No. 18 needle placed through the skin into a femoral vein.

After it was functioning well, 20 cubic centimeters of 70 per cent urokon were injected as rapidly as possible and 3 successive films made (ending 12 seconds postinjection). Later it was learned that good films could be made by injecting 20 cubic centimeters of 70 per cent urokon into a saphenous vein and exposing the film at the end of injection. A still later technical refinement placed the dog in an oblique position so that the cava would not be superimposed upon the vertebrae. It was never necessary to "cut down" in order to cannulate a vein for venography. Figure 2a illustrates a normal venogram, without dye in the collateral veins. Figure 2b and c shows 2 different dogs which had what was thought to be adequate caval ligation. The x-ray films, however, showed the dog in Figure 2b to have a bifid vena cava just at the ligation site. These observations indicated the importance of a dissection to expose such situations, and after this experience the exposure was deliberately increased prior to ligation.

The anticoagulant. Tromexan was administered to 10 dogs. A dosage of 17.1 milligrams per kilogram was given by mouth just prior to operation, and postoperative doses were given by mouth for 7 days to evaluate the effect on thrombosis caudad to the caval tie. Postoperative doses were based on daily prothrombin times in an effort to maintain these at between 20 and 40 per cent. This regimen was based upon our use of tromexan clinically, and prothrombin determinations were done in the clinical laboratory.



a b c

FIG. 2. Urokon venograms of dogs showing: a, normal; b, bifid vein allowing dye to by-pass ligature at arrow; and c, large direct collateral by-passing ligature at arrow.

Autopsy. Autopsy examination was performed on only the abdominal contents and veins in animals which were intentionally sacrificed. In most instances, the cava and its tributaries were dissected out carefully, and one end was injected with water prior to opening and pinning it flat for photographs, fixations, and microscopic sections. Several attempts to make a latex rubber mold of the inside of the cava and its tributaries were unsuccessful, but several excellent vinylite casts were made of specimens by Charles Tobin of the Anatomy Department. Complete examination (omitting the brain) with selected microscopic study was done on dogs that died prior to sacrifice.

Clinical experience. Since January 1955, based on this investigation, 5 patients surviving initial embolism have had inferior vena caval ligation with No. 00 chromic gut. A brief account of these patients will be presented later.

DISCUSSION OF RESULTS

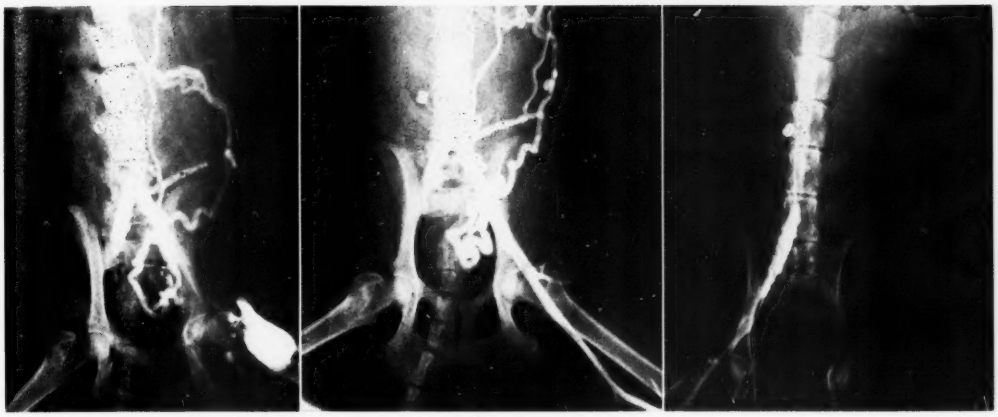
Deligation of vena cava. Table I shows the entire experimental series. Twenty-seven dogs survived for over 10 days after either high or low ligation. Two died of distemper at 20 and 22 days respectively with the cava still ligated. Twenty-three of the remaining 25 (92 per cent) showed x-ray and autopsy deligation and luminal reconstitution of the cava. The animals of groups 3 and 4 are not included in this 92 per cent deligation calculation since deligation was impossible if a part of the vein was excised and very unlikely when lumbar veins were tied at the same time because of the extensive thrombosis that the procedure produced. Streuter and Paine noted 82 per cent recanalization following caval ligation with several sizes of gut. Both series, therefore, indicate that a high percentage of animals do show reconstitution of the vena cava after absorbable gut ligation.

The deligation time in Table I shows the day of the last venogram indicating occlusion of the vena cava and of the first venogram indicating reopening. In some instances, there was a longer period of time than should have elapsed between venograms. For example, in dog 53–175 the last

TABLE I.—SUMMARY OF 55 DOGS STUDIED

Dog	Ligature size	Deligation time, postoperative days	Total days observed	Cause of death	Distal thrombosis by venogram	Cava at autopsy
				GROUP 1. HIGH LIGATION, 19 DOGS		
52–186	2	101–142	340	Sacrifice	Yes	Stricture, distal organized thrombus
53–67	2	271–307	356	Sacrifice	Yes	Stricture
53–145	00	135–185	272	Sacrifice	Yes	Stricture, distal organized thrombus
53–167	00	130–158	185	Sacrifice	Yes	Stricture
53–175	00	15–121	181	Sacrifice	Yes	Slight stricture, small distal organized thrombus
54–40	00*	232–265	421	Sacrifice	Yes	Web at stricture
54–35	00*	54–62	94	Sacrifice	Yes	Stricture
54–381	00	56–121	193	Urokon injection	No**	Web at stricture
54–415	00	21–106	217	Sacrifice	No**	Wide open
54–394	00	125–170	209	Sacrifice	No**	Stricture, no thrombosis
54–422	00	29–93	203	Sacrifice	No**	Web at stricture
54–449	00	7–85	172	Sacrifice	No**	Stricture
54–345	00	—	6	Anticoagulant; bleeding	No**	Tiny distal thrombus
54–350	00	—	1	Massive aspiration	No**	No thrombosis
54–405	00	—	1	Anticoagulant; bleeding	No**	Distal soft thrombosis
53–34	2	No	684	Sacrifice	Yes	Extensive thrombosis
53–143	00	—	1	Urokon injection	No	No thrombosis
54–39	00*	No	489	Living pet	Yes	—
53–170	00	—	22	Distemper	Yes	Distal thrombosis
				GROUP 2. LOW LIGATION, 22 DOGS		
53–210	00	18–94	131	Sacrifice	Yes	Stricture, distal organized thrombus
53–273	00	79–133	137	Sacrifice	No	Large lumen, no thrombosis
53–353	00	112–132	178	Sacrifice	?	Stricture
53–361	00	56–113	117	Sacrifice	?	Web at stricture
53–413	00	37–66	131	Sacrifice	Yes	Open, cast unsuccessful
53–415	00	172–209	209	Sacrifice	No	Open, no thrombosis
54–1	00	51–97	230	Sacrifice	No	Web at stricture
54–37	00	66–100	161	Sacrifice	?	Open lumen (Fig. 5 cast)
54–33	00	154–191	195	Sacrifice	No	Stricture at left iliac vein
54–63	00	36–78	141	Sacrifice	No	Open lumen (Fig. 5 cast)
54–76	00	69–125	169	Sacrifice	Yes	Tight stricture
53–199	00	—	20	Distemper	Yes	—
53–391	00	—	6	Distemper	No	No thrombosis
53–225	00	—	9	Distemper	No	—
52–7	2	—	4	Postop.	No	No thrombosis
53–136	00	—	1	Postop.	No	No thrombosis
53–98	00	—	1	Postop.	No	No thrombosis
53–365	00	—	1	Postop.	Yes	Soft distal thrombus
53–343	00	—	2	Postop.	No	No thrombosis
53–358	00	—	1	Postop.	No	No thrombosis
54–75	00	—	1	Postop.	No	Pneumonitis; no vascular thrombi
54–210	00	—	1	Postop.	No	—
				GROUP 3. HIGH + LUMBAR VEIN LIGATION, 9 DOGS		
53–379	00	51–108	112	Sacrifice	Yes	Organizing thrombosis of cava and iliacs
53–412	00	No	26	Sacrifice	Yes	Organizing thrombosis of cava and iliacs
53–375	00	No	329	Sacrifice	Yes	Complete thrombosis of distal cava
53–395	00	No	351	Sacrifice	Yes	Complete thrombosis of distal cava
54–269	00	—	2	Postop.	?	No thrombi in vessels
54–290	00	—	2	Postop.	No	No thrombi in vessels
54–324	00	—	7	Postop.	?	Thrombus in cava
54–445	00	—	1	Anticoagulant; hemorrhage	No**	No thrombosis
54–425	00	—	1	Anticoagulant; hemorrhage	No**	No thrombosis
				GROUP 4. CAVAL EXCISION, 5 DOGS		
52–82	00	—	93	Sacrifice	No	No thrombi in vessels
53–351	00	—	104	Sacrifice	?	No thrombi in vessels
52–197	00	—	?	Sacrifice	No	?
53–373	00	—	1	Postop.	No	—
53–380	00	—	1	Postop.	No	Small distal thrombus

*Double loop ligature.
**Use of tromexan.
Deaths marked postoperative mean no discernible cause other than blood pooling in lower body.



a b c

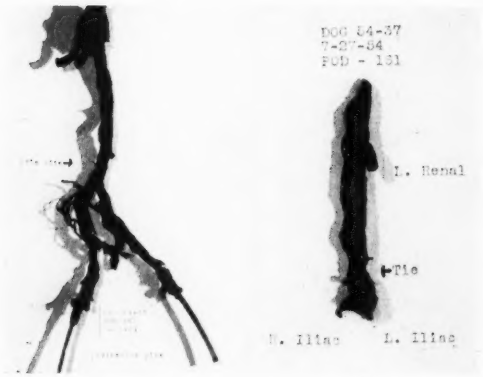
FIG. 3. Deligation and recanalization of vena cava in dogs. a, Shows dilated collateral veins and rounded dye pattern at site of ligation 51 days postoperatively; b, 97 days postoperatively, dye passes through ligation site; c, 171 days after operation, widening of caval lumen since film in b. Collateral veins have disappeared.

venogram showing the cava closed was made on the fifteenth postoperative day. The next x-ray examination was delayed until 121 days after operation and showed the caval lumen to be reconstituted. The deligation, therefore, occurred at an unknown time between the fifteenth and one hundred and twenty-first day after ligation. For this reason it seems useless to calculate the average deligation time represented in this series.

Streuter and Paine found a 41½ day (6 weeks) average opening time in the dogs subjected to chromic gut caval ligation. Their report indicates that in 20 (59 per cent) of the 34 dogs in their series showing deligation reopening was proved by venography to have occurred before the fiftieth postoperative day. We had no roentgenographically proved instance of this early deligation. Streuter and Paine reported only 1 instance (4 per cent) of a venogram after the fiftieth day showing caval occlusion while we had 14 such instances (64 per cent). This analysis indicates that our experiments resulted in considerably later deligation than theirs.

The cause of this difference in time of deligation is not clear. Our technique of ligation was somewhat different since we usually used a single loop ligature instead of a double loop. No. 00 gut was used by us while Streuter and Paine used No. 2 or No. 0 gut. The third difference was that in their dogs the lumbar veins also were tied. The most likely cause for the time difference appears to lie in the interpretation of the venograms. It is admittedly difficult to determine whether a thin dye stream penetrates the ligation site. Our deligation times are based upon films that show such penetration without question, which fact undoubtedly leads to error on that side. From a practical standpoint it would seem that the cava should optimally remain ligated until distal thrombi had become fixed to the vein wall and organized so that no later emboli would occur. None of the experimental series have shown such evidence.

The 2 cases in which the cava failed to reopen deserve comment. In each instance there was notable distal caval thrombosis which may explain failure of reconstitution of the lumen. The dogs in which the lumbar veins also were all ligated may shed light on this, for there was extensive thrombosis in all that survived the immediate postoperative period. Only 1 of those 4 dogs showed



a b

FIG. 4. Vinylite casts of deligated vena cavas. a, 141 days after ligation; b, 161 days after ligation.

caval deligation which suggests that extensive thrombosis tends to prevent luminal reconstitution.

The process of deligation and caval luminal reconstitution appears to be a gradual one, as described by Miles and Young. Figure 3 illustrates the venographic appearance soon after deligation when a tiny stream of dye passes through the site of ligation. This small initial opening increases with time, coincidental with a more regular appearance of the wall of the vein.

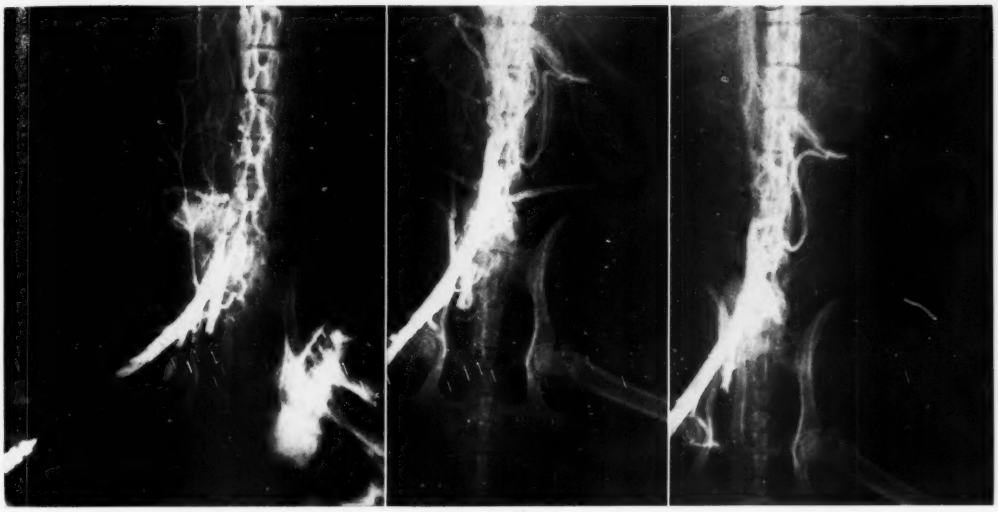
Gross examination of multiple dogs shows that at first there are multiple tiny openings at the ligation site which probably increase in size and coalesce, reproducing the process of recanalization of a thrombus. Some specimens and casts at a later date show a larger lumen traversed by a few strands of fibrous tissue coursing from wall to wall of the cava. The usual findings at sacrifice following deligation shown by venography consisted of slight external fibrosis at the ligation site and a stricture of the vena cava. At the actual ligation site there was usually narrowing with fine strands of fibrous tissue coursing from the walls across the lumen. Later follow-up x-ray films showed gradual widening of the lumen. In some instances the lumen was narrowed scarcely at all. Figure 4 shows 2 vinylite casts of such results.

Thrombosis distal to ligation. Of the 31 dogs surviving either high or low ligation for 48 hours, 13 showed definite x-ray or autopsy evidence of significant thrombus formation caudad to the ligation site. This 45 per cent thrombosis represents a minimal possible incidence, because some of the 18 nonthrombosing animals died soon after operation when differentiation between antemortem and postmortem thrombosis was difficult. Three were questionable by venogram. Some dogs received tromexan, as will be discussed.

Thrombosis was apparent on the venogram by failure of the dye to penetrate up the vein to the ligation site as seen in Figure 5a. Early in our experience it was suggested that such a film might indicate poor filling rather than thrombosis. However, correlation of the venographic findings with those at autopsy, the later disappearance of parts or all of such venographic changes, and their complete absence in dogs receiving tromexan indicates that such pictures do indicate thrombosis. Gross examination following early postoperative death in certain instances showed a soft, jelly-like thrombus lying loosely within the cava (Fig. 6). Contrary to the report by Miles, this distal thrombosis has often been found to extend beyond the first collateral (lumbar) vein and often to extend into these lumbar veins as well as into the tributaries of the iliac veins (Fig. 7). The growth rate of this thrombus is undetermined.

Later examination by venography shows increasing penetration of dye toward the ligation site (Fig. 5b), and finally the deligation (Fig. 5c). Gross examination now shows (Fig. 7) a firm, fibrous, whitish thrombus which is firmly attached to the wall of the vein.

In no instance in these dogs was there evidence of pulmonary embolism occurring after caval deligation. Inspection of the firmly attached, well organized thrombi found at sacrifice of the animals indicates little likelihood of emboli from the original thrombus. It is believed generally that pre-



a b c

FIG. 5. Repeated venograms at 3, 45, and 142 days after operation showing change in collateral venous pattern. Left venogram shows dye about tail of thrombus extending into right iliac vein at lower arrow. Upper arrow indicates ligation site.

vious thrombosis predisposes to recurrence later. The question of whether the deligated and open cava which has irregular scarred walls will later develop recurrent thrombosis has been properly raised. We see no method to test this possibility in the laboratory and believe the solution of the problem must await careful follow-up examinations of patients undergoing the procedure. Our 5 clinical patients are too recent to allow long term evaluation.

Anticoagulants after ligation. Distal thrombosis was quite impressive to us. It was found in similar experiments by Moretz and his associates and by Streuter and Paine. Clinical experience indicates that it occurs often in humans subjected to caval ligation. Recently obtained venograms in 4 patients support this belief. It was, therefore, decided to test the effect of an anticoagulant upon its occurrence.

Ten dogs were given oral doses of the anticoagulant tromexan prior to operation. Eight dogs had high ligations, 2 dogs had high ligations associated with lumbar ligation. It proved not too difficult to manage the anticoagulant so that the prothrombin time lay within the desired 20 to 40 per cent range without producing uncontrolled bleeding. The first dog subjected to high ligation and anticoagulation died on the sixth postoperative day as a result of uncontrolled bleeding. Four dogs died in the immediate postoperative period of 24 hours: 1 of severe aspiration pneumonia; 3 of massive interstitial hemorrhage below the site of vena cava ligation, 2 of these being dogs with high plus lumbar ligation. Five consecutive dogs had high ligation followed by successful anticoagulation. None of the dogs in the tromexan series showed any evidence of thrombus longer than a few millimeters caudad to the tie. The 66 per cent distal caval thrombosis in groups 1 and 2 (24 dogs) when tromexan was not used may be contrasted with the 6 dogs without thrombosis when tromexan was administered for 7 days after operation. Three indeterminate nontromexan animals are omitted. The 66 per cent thrombosis mentioned is a corrected incidence while the 45 per cent noted before is the overall minimum incidence.

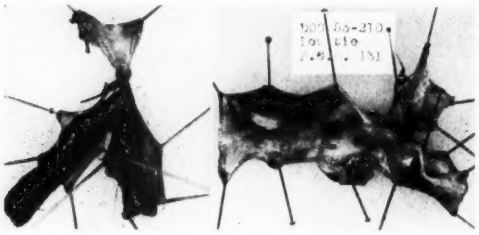


FIG. 6.

FIG. 7.

FIG. 6. Opened vena cava and iliac veins of dog dying 12 to 16 hours after low ligation showing soft cast-like thrombus.

FIG. 7. Opened vena cava of dog sacrificed 131 days after caval ligation with No. 00 chromic gut. Lumen constricted but open at ligation site. Note firm, well attached whitish thrombus in opened iliac vein.

Venograms of the anticoagulated survivors showed a quite different intraluminal pattern than the previous larger series, none of which had an anticoagulant drug. Figure 8 shows dye penetration clearly to the ligature site on the fourteenth postoperative day in a dog treated with tromexan for 7 days after operation. This finding contrasts markedly with the usual picture in those dogs not given tromexan, of which Figure 5a is a typical example. The drug was stopped after 7 days without the later development of thrombosis.

This small series, therefore, suggests that anticoagulants such as tromexan prevent caval thrombosis distal to the ligation. All these animals that survived had later deligation of the cava. This combined with the evidence already mentioned that extensive thrombosis may tend to prevent luminal reconstitution suggests the use of anticoagulant drugs following a temporary caval ligation.

Collateral venous circulation after ligation. The venograms of Figure 5 show the extensive collateral circulation which develops after caval ligation. This may be contrasted with the venogram of Figure 2a in which the cava had not been ligated and in which no collateral veins are outlined. Pathways of venous blood return following caval ligation have been described by Northway and Buxton and by Robinson and will not be recounted. Caval ligation in these dogs produced visibly distended abdominal veins as can be observed in humans.

Six dogs had technically satisfactory venograms the day of operation. In each case there was good filling of the vertebral veins. The hip, pelvic, and abdominal collateral veins were usually seen as thin streams of dye or as a fine tracery. After several days the vertebral veins were little changed in appearance, while the other collateral veins showed increased size and beginning tortuosity. Later examinations showed a change from multiple small veins present over a wide area to a few large dilated veins lying closer to the site of ligation. Figure 5 illustrates this change in pattern.

Study of the venograms indicates to us that, in the dog at least, the vertebral veins immediately serve as alternate pathways for venous return and do not change size with time. The hip, pelvic, and abdominal veins, however, are small and require time to reach their maximum luminal size, at which time they tend to become tortuous. With more time the dye flows through a few large collateral veins instead of being widely distributed via multiple small veins.

Coincidental with resumption of patency of the inferior vena cava the collateral venous pattern (by venography) disappeared. Evidence of this fact in the face of a technically poor venogram at the site of ligation several times prompted immediate repetition of the venogram at which time the cava was found to be open. In Figure 5 this disappearance of collaterals is illustrated.

Venous pressure following ligation. Figure 9 indicates the average venous pressure response to ligation of the vena cava at the high and low sites. Individual animals were quite variable and the saphenous venous pressure rose as high as 1,400 millimeters of saline in 1 instance. In each there was a sharp initial rise which then decreased slowly until stability at about 1 hour.

Although the initial average pressures of the high and low ligation groups were quite different, both appear to stabilize at approx-

imately equal pressures. We interpret the first portion of these curves as indication of the relative lack of collateral venous channels after low ligation as opposed to high ligation. With time this factor appears to lose its importance.

In order to investigate the difference further a series of 8 dogs had temporary occlusion of the cava at the high site and a 30 minute study of venous pressure response, followed by release of occlusion and a second occlusion at the low site. Inspection of the individual records indicates that, as the average curves of Figure 10 show, the release of caval occlusion and reapplication of it at the low site did not usually cause a particular rise in venous pressure, although it did in a few. The second pressure curve appears to follow the initial one.

The curves are interpreted as evidence that the initial caval occlusion results in distal venous hypertension with opening of collateral venous pathways, which are still open when the site of occlusion is changed. It was expected that the low ligation (with loss of lumbar veins as outlets for blood under pressure) might lead to a new peak of pressure. This occurred occasionally but not as a rule. Usually the first peak could not be reproduced.

Figure 11 shows, on the left, the average of venous pressure studies of 28 dogs and, on the right, of 19 of these dogs after deligation (using that time as a new zero point). The animals which did not show deligation are not included on the graph beyond the 210 day time. Despite the report of Nabatoff and associates to the contrary, our findings are similar to those of Moretz, Naisbitt, and Stevenson that the venous pressure of the lower limbs remains elevated over a long period. No sharp decrease was found at the time of deligation, but rather a persistent fall toward control levels. The majority of animals were sacrificed soon after the cava was proved open by venogram, and control levels were seldom reached.

Clinical manifestations. Some of the animals showed pitting edema of the legs and lower abdomen in the immediate postoperative period. None continued to have edema if they survived over a week. Dilated abdominal veins were apparent regularly if the hair was removed. An occasional animal had temporary hematuria. It was our impression that these evidences of venous hypertension were more apt to occur after low caval ligation, but no actual analysis of this was made.

FIG. 8. Venogram made 14 days postoperatively of dog receiving tromexan therapy for 7 days. Note smooth filling of dye to point of high ligation. No thrombosis.

The postoperative pattern followed one of two courses. Most of the animals recovered and behaved like any dog having a laparotomy with the occasional addition of the effects mentioned. Some animals were found dead in their cages without any position change to indicate that consciousness was regained after operation. Others became conscious but were lethargic and appeared moribund until death. These cases will be discussed.

Survivors appeared to walk and exercise normally, although no exercise tests were done.

Deaths after caval ligation. Twenty-four dogs died prior to sacrifice: One fatality due to urokon followed a second injection of 20 cubic centimeters of a 70 per cent solution after failure of the first to delineate the veins properly in an animal operated upon 2

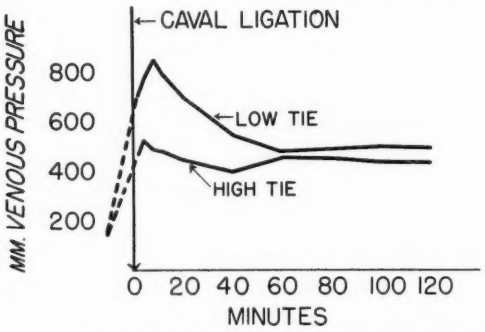


FIG. 9. Average saphenous venous pressures following high and low caval ligation. All pressures were read from the level of the table under the dog.

hours previously. This animal ceased respiring as the injection ended. Another death occurred following an injection of urokon 193 days postoperatively. One death was due to aspiration of gastric content on the operative day, and another to hemorrhage after tromexan on the sixth postoperative day. Four dogs had a clinical syndrome judged to be distemper and were found dead or sacrificed. Two animals were found dead on the fourth and seventh postoperative days respectively; no cause of death could be found at autopsy. The other 14 deaths occurred either the afternoon or night after operation and appeared similar to the deaths observed by Moretz, Naisbitt, and Stevenson.

They collected several instances of shock or death following vena caval ligation in

TABLE II.—POSTOPERATIVE MORTALITY WITHIN 48 HOURS BY SITE OF LIGATION OF VENA CAVA

Ligation site	*No. of dogs*	*No. of deaths*	*Mortality, per cent*
High	17	1	6
Low	22	8	36
High + lumbars	9	5	56
Excision	5	2	40

TABLE III.—MINIMAL SAPHENOUS VENOUS PRESSURE ATTAINED IN THE 2 HOUR PERIOD AFTER CAVAL LIGATION

	Saphenous venous pressure		
Ligation site	*Less than 600 mm.*	*Greater than 600 mm.*	*Per cent greater than 600 mm.*
High	10	2	17
Low	16	7	30
High plus lumbars	3	3	50
Excision	2	1	33

continuity in humans, and added a personal case. Eight of their 40 dogs died in the early postoperative period with a syndrome like phlegmasia cerulea dolens. They suggested inadequacy of venous return resulting in circulatory failure. We agree that this seems to be the explanation of such deaths. Following are reported further analyses of the venous pressures in relation to this. However, while they found continued elevated femoral venous pressure in dogs that died, we have been unable to predict death by this means, as will be discussed. Fifty-five per cent (6 dogs) of the animals with lowest venous pressure within 2 hours postoperatively of over 600 millimeters of saline lived and 45 per cent (5 dogs) died. On the other hand, 19 per cent of the 31 dogs with low pressure did die. It should be noted that our measurements of pressure were made via the saphenous vein while theirs were from the femoral vein. We have twice simultaneously recorded iliac and saphenous pressures for 2 hours after ligation and found no great difference, so believe that the femoral pressure would not be different. It may also be noted that Moretz, Naisbitt, and Stevenson emphasized that all the deaths in their series had in common the presence of a needle in the femoral vein for several hours. All our measurements were made via saphenous vein in which the needle is believed to be innocuous. Our similar pattern of deaths makes us doubt that the femoral vein needles had anything to do with the deaths which occurred in their series.

Streuter and Paine reported no deaths following caval ligation in dogs. We believe the explanation is that they tied high above some lumbar veins, which in our experience is a safe procedure compared to low ligation below all lumbar veins. The importance of the site of ligation has not been previously investigated, but in dogs, at least, it influences the risk greatly.

For purposes of analysis of our mortality percentages by site of ligation we have excluded from consideration the 2 deaths from

urokon, 1 aspiration, and 2 unknown causes. The 4 deaths from distemper and 1 from hemorrhage were counted as surviving the immediate postoperative period. Thus, in Table II there are 16 deaths prior to 48 hours after operation.

The single death in a dog whose cava was tied high was in an animal treated before operation with tromexan. Autopsy showed extensive hemorrhage in the soft tissues of the abdominal wall and retroperitoneal areas caudad to the site of ligation.

Eight immediate postoperative deaths occurred following low caval ligation caudad to all lumbar veins. This fact indicates some difference in the risk of high and low caval ligations in dogs. Since the lumbar veins are available as collaterals to return blood from the lower body after a high ligation it appeared that their availability for this might directly influence the risk.

In a new series of 9 dogs, therefore, the usually safe high ligation was done. At the same time all lumbar veins caudad to the ligation were tied with silk close to the cava. Five of these dogs died to produce a 56 per cent immediate postoperative mortality. This result indicates to us the danger of ligation without open lumbar veins distal to the site. In dogs, therefore, low ligation is more dangerous than high ligation.

It has been thought that death might be predicted soon after caval ligation by study of the immediate venous pressure response. Thus, if the venous pressure did not soon greatly diminish from its peak after caval ligation, this might predict that the collateral channels for venous return would not at once be sufficient to drain blood from the lower body so that pooling would occur, with consequent lack of venous return to the heart leading to vascular collapse. The immediate postoperative venous pressure responses of these dogs were therefore analyzed.

Table III shows that for the 2 hour period after caval ligation any type ligation can produce a high or low saphenous pressure

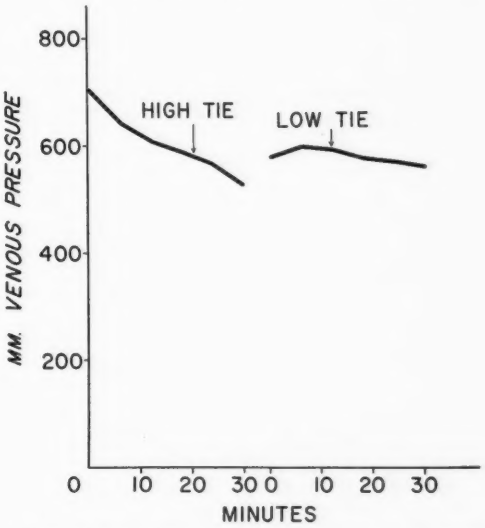


FIG. 10. Average saphenous venous pressures of 8 dogs having high occlusion of the cava for 30 minutes followed by low block.

response. (The 600 millimeter saline level was arbitrarily selected as the dividing line after inspection of records.) However, a high ligation that allowed the lumbar veins to remain intact caudad to the tie was somewhat less likely to produce this immediate sustained high venous pressure. While high ligation produced only 17 per cent of pressures over 600 millimeters of saline for 2 hours, low ligation caused 30 per cent and high plus lumbar ligation caused 50 per cent high venous pressure. We interpret this to indicate somewhat more likelihood of

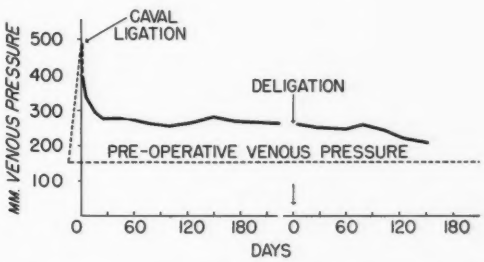


FIG. 11. Average saphenous venous pressures in 28 dogs after caval ligation. After the second zero point there is continued decrease in pressure in 19 of the dogs followed for a period after deligation by venography.

TABLE IV.—PATIENTS HAVING ABSORBABLE GUT LIGATION OF INFERIOR VENA CAVA FOR PULMONARY EMBOLISM, FEBRUARY TO NOVEMBER 1955

Patient	*No.*	*Age*	*Sex*	*Primary diagnosis*	*Follow-up period*	*Further embolism*	*Leg edema*		*Other comment*
							Preop.	*Postop.*	
H.G.	390336	70	M	Ca. of rectum	85 days	0	None	None	Died 85th day
F.C.	359548	72	M	Acute cholecystitis	7½ mos.	0	Yes	Yes	Alive and well
G.B.	83914	63	M	Phlebitis	9 mos	0	None	None	Alive and well
O.B.	391681	42	F	Ca. of ovary	2 mos.	0	Slight	None	Alive and well
R.C.	201063	23	M	Phlebitis	5 wks.	0	None	Yes	Alive and well

high sustained pressure after low than after high caval ligation in dogs.

The early mortality associated with the lowest saphenous pressures was recorded within 2 hours after caval ligation (any site). If venous pressure was sustained over 600 millimeters saline there was 45 per cent mortality in 11 dogs. If venous pressure fell below 600 millimeters saline there was 19 per cent mortality in 31 dogs. Similarly different mortality rates were found by separating the animals at somewhat different pressure levels. This observation indicates to us that higher pressure response is associated with more risk to the dog. However, it is important to notice that deaths did occur when the pressure was low and there were survivors with high pressures, so that it was impossible to make an absolute prediction.

This analysis indicated inability to predict the risk in an individual dog when venous pressure was followed for at least 2 hours after ligation. Since one would not be able to study a patient on the operating table for 2 hours before deciding whether ligation was safe, the series was analyzed for mortality correlation to a 30 minute study of pressure. The following figures show that this analysis is even less valuable: Of 20 dogs with venous pressures of less than 600 millimeters of saline, 5 (25 per cent) died. Of 15 with venous pressures of greater than 600 millimeters of saline 5 (33 per cent) died. We, therefore, believe that such study (in dogs at least) will not be of help in predicting the ones who will not safely tolerate caval ligation.

In 5 patients studied to date the existence of venous thrombosis prior to operation was associated with elevated saphenous pressures before ligation, with quite variable postligation response. At present, therefore, it is believed that these pressures should be studied in patients, but that no positive correlation with operative mortality has yet been found. There has been no operative mortality with caval ligation in this hospital, although such has been reported elsewhere. Moretz, Naisbitt, and Stevenson have not yet reported clinical experience with their method of placing a removable metal clip on the cava. It is possible that such a clip could be removed if the clinical course after caval ligation indicated a grave prognosis. On the other hand, if early thrombosis had already occurred, immediate clip removal might result in embolization of such a thrombus.

Our present clinical plan, therefore, is to study the saphenous venous pressure in both legs during caval ligation, but to perform the ligation regardless of pressures obtained so long as the patient's condition, as measured by blood pressure, pulse, and appearance remains satisfactory during a 5 to 10 minute period of temporary caval occlusion prior to actually tying the ligature. Further observations are needed to determine whether this short test period will be of value.

Clinical experience. Our laboratory studies appeared to furnish a sound background for evaluation of caval ligation by absorbable gut in patients. The chief objections seemed to be, first, the possibility of later pulmonary embolism and second, some doubt that the tie would occlude the cava long enough for all distal thrombi to become firmly attached. There had been no evidence of later embolism in dogs in our series or others, and the advantages of caval deligation seemed

great enough to warrant the trials necessary to determine this point clinically. Streuter and Paine's series of dogs showed considerably earlier caval deligation than ours for unknown reasons. In our experience, the distal clots (when they occurred) were always firmly attached at the time of deligation. Also, at initial deligation and lumen reconstitution the opening was tiny and often consisted of multiple openings through strands of fibrous tissue, so that the likelihood of an immediate massive embolus seemed remote. Despite theoretic fear of emboli our chief concern actually was whether the tie would come off and allow caval recanalization to occur with the lowering of venous hypertension in the legs of patients.

We have, in general, depended upon anticoagulants to treat venous thrombosis and pulmonary embolism and have reserved venous ligations for those few who had recurrent embolism or contraindication to anticoagulants. A survey of all autopsied patients for a 1 year period in the Strong Memorial and Rochester Municipal Hospitals has indicated continuation of this general policy. In the past, most venous ligations were directed toward the superficial femoral veins, but recently, inferior vena caval ligation has been done more often.

On the basis of this investigation the 5 caval ligations have been done to date in 1955 with absorbable gut. These cases are summarized in Table IV. All patients tolerated the operation well. No further embolization has occurred to date. The table indicates preligation and postligation edema, although none have yet been followed very long.

Urokon venograms were done prior to hospital discharge in 2 patients without carcinoma (who can be followed for a long period). These both showed collateral circulation with complete caval occlusion. These x-ray studies will be repeated later.

Three of these patients have received postligation anticoagulants, starting 3, 2, and 1 day later respectively. Leg edema seen despite this treatment suggests to us that anticoagulants must be started sooner than has been done.

SUMMARY

Temporary inferior vena caval ligation using absorbable gut resulted in a high percentage of later deligation and recanalization of the venous lumen in dogs as denoted by venograms and autopsies. Occasional failure of caval reconstitution was usually due to extensive distal venous thrombosis. This could be prevented by early postoperative use of tromexan.

Urokon venograms showed the change with time from many, fine, scattered venous collaterals to a few, large direct ones, with disappearance of all when the cava reopened.

Saphenous venous pressure was initially quite elevated but returned to a stable elevation at about 1 hour after ligation. A gradual decrease occurred after caval deligation.

Some dogs died after caval ligation presumably from venous pooling in the caudal parts of the body and legs. Low caval ligation just above the iliac veins was more dangerous than high ligation above several lumbar veins. The association of prolonged saphenous venous hypertension with death was analyzed. Study of pressure in the individual animal, however, did not always predict its survival or death.

Five patients have quite recently been operated upon by this technique without mortality. Further study of these and other patients will be necessary to determine the usefulness of absorbable gut caval ligation in the human.

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HEMANGIOMAS OF THE EXTREMITIES

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HEMANGIOMAS occur in every tissue of the body except the hair and the nails. These benign, blood vessel tumors appear in females two or three times as often as in males, and also occur more commonly among patients who are less than 30 years of age than among those who are 30 or more. Bailey and Kiskadden stated that a half to a third of all infants are born with some cutaneous vascular anomaly. Whether or not this estimate is correct, the fact still remains that hemangiomas are common tumors.

The belief that hemangiomas are congenital has seemed easy to substantiate because of: (1) their predilection for the branchial clefts, (2) the large number of them seen at birth, and (3) other directly traceable congenital factors. As mentioned subsequently, independent tumors have been produced by injecting carcinogens into specific strains of mice. Two such hemangiomas were passed through 20 generations of mice. Thus, in part at least, the idea that hemangiomas are congenital must be revised.

Recently, 93 cases of hemangioma encountered at the Mayo Clinic were reviewed. In these patients the tumors were on the extremities and all were treated surgically. They were classified as either discrete or diffuse. Diffuse tumors were defined as those that: (1) could not be removed at one surgical "sitting," (2) were composed of more than one coalescent mass, or (3) were greater than 12 inches (about 30 cm.) in diameter. Tumors were considered to be discrete if the foregoing criteria did not apply. In 20 of the 93 cases the hemangiomas were diffuse and in 73, discrete.

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The history and physical findings in the 73 cases of discrete tumor were reviewed. The situation of the tumors in the body is represented in Figure 1. The symptoms and physical findings most frequently encountered in 73 cases of discrete hemangiomas of the extremities were: Symptoms—tissue mass in 91 per cent; pain in 65 per cent; swelling in 54 per cent; cosmetic change in 49 per cent. Physical findings—palpable tissue mass in 95 per cent; discoloration of skin in 53 per cent; tenderness in 47 per cent; change in color, size, and prominence on dependency in 9 per cent. Pain and the presence of a tissue mass were the commonest symptoms, while the presence of a palpable tissue mass was the commonest physical finding.

The diffuse tumors were of such size that charting of their situation in the body was not rewarding. The symptoms and physical findings encountered in the 20 cases of diffuse hemangioma were: Symptoms—tissue mass in 75 per cent; pain in 75 per cent; swelling in 85 per cent; cosmetic change in 70 per cent. Physical findings—tissue mass in 95 per cent; discoloration of skin in 60 per cent; tenderness in 80 per cent; change in color, size, and prominence on dependency in 40 per cent. Painful swelling and a tissue mass, either or both, with obvious cosmetic change, seemed the commonest features of the history, while a tender tissue mass was most often found on physical examination.

In each of the 93 cases, a surgical specimen was examined for gross and microscopic pathologic changes. On inspection, the tissue of the tumors varied in color from bluish red, or purple, to reddish brown or reddish gray. Cut sections grossly resembled sponges distended with blood. On palpa-

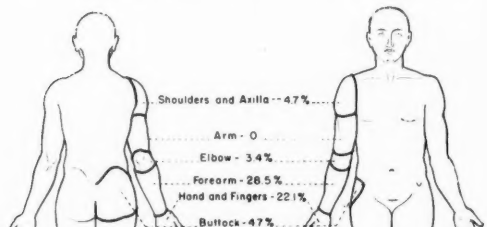


FIG. 1. Location of discrete hemangiomas revealed on physical examination.

tion, a mushy or gritty sensation was noted. The diffuse hemangiomas ramified widely over the involved extremities. On the other hand, the discrete tumors were well localized—some even had capsules—and averaged 4.9 cubic centimeters in size. Grossly, all of the diffuse hemangiomas invaded the adjacent normal tissues, while only 23 per cent of the discrete tumors showed this trait. Gross characteristics are represented in Figures 2 and 3.

Microscopic differences between diffuse and discrete tumors were not noted. As is known, hemangiomas are of capillary type or cavernous type. A capillary tumor is composed of many small capillary buds which are about to form blood spaces, while a cavernous tumor is composed of large, endothelium-lined, blood-filled spaces (Fig. 4a and b). Of the surgical specimens in these 93 cases, 22 per cent were solely capillary in type, 52 per cent were solely cavernous in type, and 26 per cent were of a combined capillary and cavernous type.

The complaint of pain in many of the patients prompted an attempt to correlate it with gross and microscopic pathologic characteristics of the tumors. Correlation was not found, however.

Roentgenographic changes were noted in many cases. The commonest change was caused by the presence of a soft tissue tumor. This was followed closely in order of frequency by evidence of generalized osteoporosis, periosteal thickening, bony erosion, and lastly, the presence of phleboliths. The phleboliths were composed of concentric layers of varying density so that, roentgenographically, they resembled mother-of-pearl (Figs. 5, 6, and 7).

All 93 patients underwent surgical excision of the hemangiomas. After operation, 75 per cent of those whose tumors had been discrete became symptomless, but all of those whose tumors had been diffuse still had symptoms. This is excellent testimony to the magnitude of the therapeutic problem presented by diffuse hemangiomas.

Four means of treatment other than surgical removal are recognized: (1) injection directly into the tumor of sclerosing agents such as a solution of urethan and quinine hydrochloride or 50 per cent solution of glucose; (2) topical application of agents such as carbon dioxide snow; (3) radiation and radium therapy, and (4) electrocoagulation. Occasionally all treatments must be combined to accomplish the desired result.

COMMENT

It is our intent to point out herein the differences and variations seen in this series

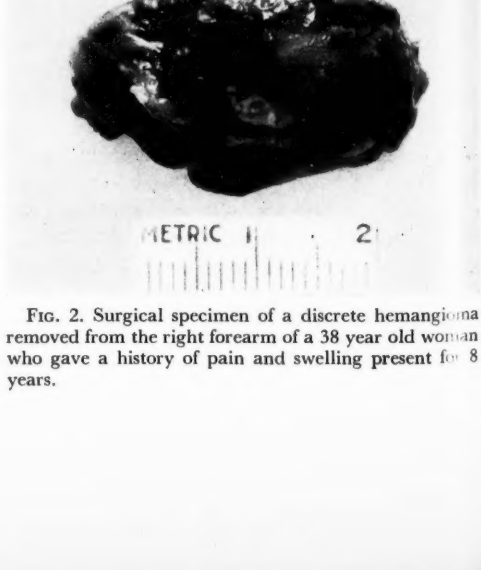


FIG. 2. Surgical specimen of a discrete hemangioma removed from the right forearm of a 38 year old woman who gave a history of pain and swelling present for 8 years.

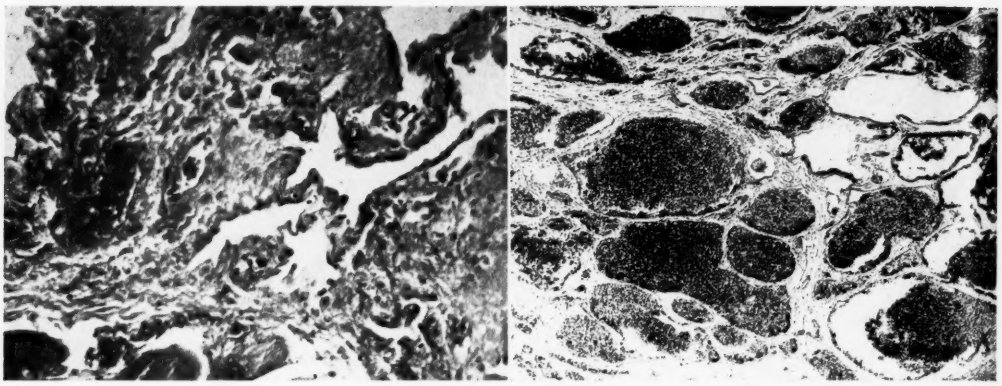
of 93 cases on comparing them with similar series appearing in the literature, rather than to re-emphasize all of the facts which were demonstrated in the review of the 93 cases.

From the standpoint of etiology, writers on the subject generally uphold the congenital theory of origin. This theory was thought to come about either by the awakening of a previously dormant congenital arrest or as a result of some congenital malformation. In 45 of the 93 cases (49 per cent) the development of the tumorous condition could not be ascribed to any cause or set of circumstances. Thirty-two patients, or 33 per cent, did state that the condition had been present at birth, but this figure is at great variance with statistics of many authors.

In 1942 Andervont and his co-workers were able to produce typical hemangiomas and hemangioendotheliomas by injections of a solution containing carcinogenic hydrocarbon (O-amino-azo-toluene) into specific strains of white mice. They noted that variations in the microscopic picture could be produced by variations in the amount of hydrocarbon injected. Furthermore, two of the hemangiomas so produced were transplanted, and both went through the twentieth generation before their growth was stopped. Histologically, these hemangiomas were indistinguishable from those occurring in the human host. A work of a similar nature was done elsewhere in 1946 with comparable results. When one considers that all of the evidence in favor of the congenital theory of origin of hemangiomas is gathered by exclusion rather than through experimental means, this mass of "evidence" pales by comparison with the incontrovertible laboratory proof of the cause of hemangiomas. Undoubtedly more work of this nature needs to be done before the final answer is gained, but the work of Andervont and his associates stands as a milestone of achievement, since it is the only concrete bit of evidence we have as to the precise etiology of these tumors.

Trauma, likewise, was believed by many authors to be an etiologic factor. In 11 (10 per cent) of the 93 cases, the patients could trace the onset of their symptoms and physical findings to a definite, well remembered, incident of trauma. It does seem logical that the trauma, no matter how severe, did suffice to bring the patient's attention to the traumatized part, and probably was instrumental in causing either an exacerbation or onset of a chain of symptoms. This effect by trauma, namely, the exacerbation of the symptoms or the instigator of the symptoms, has been mentioned in the literature. Trauma from without the body is the type most often described, but trauma from within, such as the normal play of one muscle

FIG. 3. Amputation specimen from an 8 year old girl with diffuse hemangioma of the lower extremity. Note the bowing of the tibia and the presence of hemangiomatous tissue within the muscles of the calf, about the knee joint, and within the shaft of the tibia.



a b

FIG. 4. a, Capillary hemangioma showing the developing endothelial cells imbedded in fibrous tissue stroma. Hematoxylin and eosin, ×170. b, Cavernous hemangioma. Note the rounded blood-filled spaces bordered by flattened endothelial cells, imbedded in a sparse fibrous tissue stroma. Hematoxylin and eosin, ×38.

on another, has been thought to be sufficient to cause growth of a hemangioma by Davis and Kitlowski. A case was reported of hemangioma of the soleus and peroneus muscles after an attack of grippe, and in another case the application of a cast was instrumental in causing growth of a previously dormant hemangioma. That trauma is a factor cannot be denied, but its role seems to be more as that of a catalyst rather than as an originator.

The presence of pain as a presenting symptom of so many of these tumors arouses interest. Davis and Kitlowski found this to be the foremost symptom in 81 per cent of their cases. In our series pain also was a frequent complaint, but it was not as frequent as in theirs, occurring in only 61 per cent of the 93 patients. Undoubtedly, the fact that this series contained hemangiomas which involved all structures of the extremities, while their series was concerned only with hemangiomas of the muscle, would tend to weigh the figures in favor of Davis and Kitlowski's series. Aside from its mere presence, the problem of the "why and wherefore" of this pain has never been conclusively answered. The presence of pain when the tumor can be seen microscopically to be situated in and around the trunk of a nerve does not pose any great problem in explanation (Fig. 8a). Several authors found tiny nervous filaments in the microscopic sections of these tumors and explained all pain on that basis. Davis and Kitlowski also believed that all pain could be explained thus, or on the basis of motion of the muscle, as well as the normal upright position of human beings, with resulting internal or external pressure on the tumor. These points, however, only reiterate the obvious.

Not so obvious cases with no logical explanation for the pain are encountered in any series of these tumors. The cause of pain in a completely isolated cavernous hemangioma of the subcutaneous tissue certainly cannot be explained on the basis of the nerves involved, nor will the idea of hydrostatic pressure afford the answer. In glomus tumor and vascular myoma, both related to angioma, pain is a constant and characteristic symptom. However, the presence of fine nerve filaments within these two neoplasms gives a ready explanation for the pain, whereas ordinary hemangiomas are devoid of nervous elements.

Some hemangiomas undergo spontaneous obliteration as a result of formation of phleboliths with blockage of the vascular channels and eventual fibrosis of the tumor. This was considered to explain, in part, the onset of pain in a previously painless hemangioma,

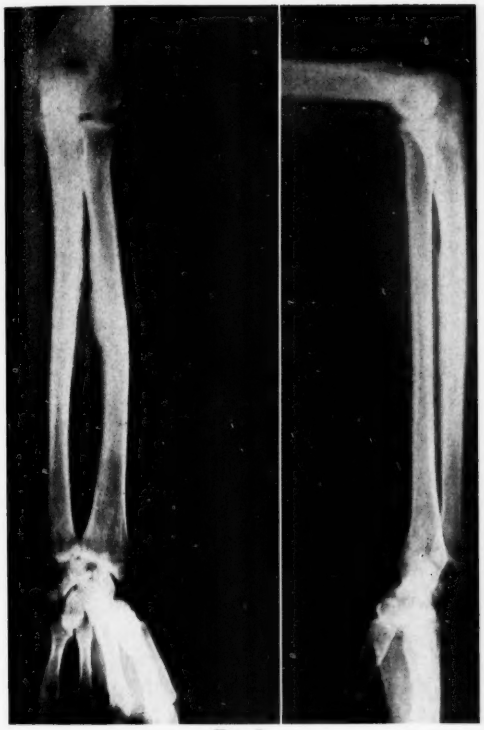


FIG. 5.

FIG. 6.

FIG. 7.

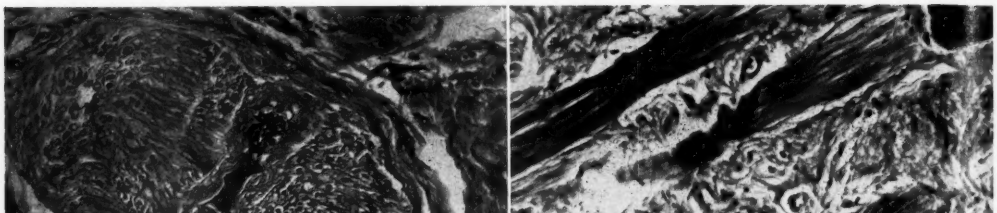
FIG. 5. Discrete hemangioma of the forearm. Note the periosteal thickening in the middle third of the ulna and the localized erosion of the radius and ulna at the site of the tumor. The surgical specimen from this case is displayed in Figure 2.

FIG. 6. Hemangioma of the forearm. Note the evidence of soft tissue swelling and the presence of the central phlebolith.

FIG. 7. Roentgenogram of a diffuse hemangioma of the leg, ankle, and foot. Note the soft tissue swelling and the rounded, lamellated character of the multiple phleboliths.

and also the stoppage of pain when once this obliterative process was complete. In this series of 93 cases we attempted to correlate pain with microscopic findings, but a definite correlation could not be made. It is true, however, that in the analysis of the cases of diffuse hemangioma thrombosis was present in a third of the patients with pain, while this change was not present in any of those without pain. This finding does not explain how the other two-thirds could have pain.

The degree of invasive tendencies, or rather the extent and presence or absence of invasion of neighboring structures, apparently had no relation to the patient's complaint of pain. In all of the diffuse hemangiomas, invasion of the adjacent structures was present, and in the discrete tumors only 14 of 42 sections taken from patients with pain showed invasion of other tissues. Hence, in some cases of hemangioma the cause of pain seems obvious; namely, invasion or encasement of a nerve trunk by neoplastic tissue.



a b

FIG. 8. a, Cross section of the posterior tibial nerve showing invasion of the nerve by hemangiomatous tissue. ×165. b, Invasion of muscle tissue by hemangiomatous tissue. Note the destruction and fragmentation of the muscle fibers by the tumor tissues. Hematoxylin and eosin, ×150.

Growth of the tumor was believed by some to be responsible for the pain, since this growth tended to encroach on adjacent structures if not actually to penetrate them (Fig. 8b). Recession of some types of these tumors also has been reported, and, because of this, some physicians have thought that none of the patients having these tumors should be exposed to treatment before they were 6 years of age in order to allow the fate of the tumor in question to be determined. In our series, none of the 93 tumors was found to have decreased in size, and only 41 per cent of the discrete and 60 per cent of the diffuse hemangiomas were seen to exhibit growth. Since pain was present in a greater number than growth, it is highly doubtful that this fact could explain the cause of pain. Also a causal relationship did not seem to exist between pain and age, or between pain and sex in this series, and this was not noted in any of the other series reviewed.

To summarize, pain still remains the enigma. In some cases its cause can be demonstrated, but in the great majority of cases one cannot predict from the microscopic or gross specimen that the patient in question had pain. The hypothesis has been put forth by Kitlowski that there was some "activator" in the system, either endocrine or otherwise, which caused these tumors to flare up at the time of puberty and of menopause and during pregnancy. This fact was examined in the light of this series, but no such finding was present. Nevertheless, this would explain, in part, the spontaneous pain in an otherwise dormant tumor, and probably would answer the problem of spontaneous obliteration. The influence of estrogens on arteriolar growth and proliferation could well be a factor in the spontaneous growth of these tumors during the three afore-mentioned periods. It remains, however, a nebulous idea that needs more investigation in order to exclude or include it as the cause of pain. At the present writing a sound explanation cannot be given to the problem of pain in hemangiomas.

The diagnostic accuracy in the case of discrete hemangioma was 43 per cent while that of the diffuse cases was 50 per cent, making an overall diagnostic accuracy of 46.5 per cent for the entire series of 93 cases. In view of the "confused" clinical picture presented by some of these cases this figure cannot be commented on too adversely. It does seem worth while, however, to attempt an improvement in diagnostic technique which will enable a correct diagnosis of these tumors more than once in each 2 cases. The triad of symptoms, namely, tumor, pain,

and swelling for the discrete tumors would tend to point the way to the diagnosis, and all that is needed from this point on is the development of some set of secondary findings or symptoms that will certify the original assumption. In the case of both the diffuse and the discrete types of tumor, the four symptoms of tumor, that is, a tissue mass, pain, swelling, and cosmetic change are foremost. Those symptoms coupled with the presence of a mass, discoloration of the skin, and associated tenderness in the discrete tumor, or a mass, discoloration of the skin, tenderness, and dependency in the diffuse tumor, ought to help further in making a presumptive diagnosis.

As to the secondary findings or "aids to diagnosis," several might be mentioned. The patient's age, sex, and body build need some consideration. Even though other authors comment on these favorably, however, this series of 93 cases has shown that they have little, if any, correlation. Location of the tumor within the extremity is of help. Eighty-six per cent of the tumors which appeared in the upper extremity in this series were situated below, or distal to the elbow, and, likewise, 57 per cent of those confined to the lower extremity were located below the knee. A considerable number of roentgenograms of the involved extremities have shown evidence of positive changes. All of the roentgenographic changes listed previously, however, could have been caused by another condition, and hence they are not specific enough for our purposes. A roentgenogram that does not show positive evidence does not rule out the existence of a hemangioma. However, if phleboliths are evident in a soft tissue mass, the examining physician again will have presumptive evidence of a hemangioma. Jones and Roberts described the peculiar configuration of phlebolith formation with a hemangioma, and, in their opinion, the appearance of phleboliths composed of concentric rings of increased density interspersed with rings of decreased density, much like mother-of-pearl, is diagnostic. The last, and probably the most positive evidence, the aspiration of blood from a suspicious-looking mass in the extremity, ought to clinch the diagnosis of hemangioma.

SUMMARY

Hemangiomas are benign, soft tissue tumors of endothelial origin and are composed of blood vessel elements in varying states of maturity. They have been known to exist since time began, and the literature contains many articles tracing their development and characteristics.

These blood vessel tumors occur among persons of all ages, but 57 per cent of the 93 patients seen at the Mayo Clinic, whose cases are reviewed herein, were less than 30 years of age. In 33 per cent of the cases the tumors were present at birth; 19 per cent were ascribed to trauma, and the remainder were of unknown etiology. However, reliable laboratory data had been presented which linked the etiology of these tumors to the carcinogenic hydrocarbons. Sex was not a factor either in etiology or in occurrence. Forty-one per cent of the tumors were in the lower and 59 per cent in the upper extremities and 20 of the 93 tumors were diffuse and 73 were discrete. Initially, 85 per cent of the patients having diffuse tumors complained of swelling in the involved extremity; 75 per cent noted pain and the presence of a tumor, and 70 per cent were concerned about the cosmetic appearance of the extremity. Sixty per cent of the patients had noted growth of the tumor. Of the patients having discrete tumors 91 per cent exhibited the presence of a mass, 65 per cent had pain, 54 per cent had swelling of the involved limb, 49 per cent had cosmetic change, and in 47 per cent the tumor had grown; the property of dependency was noted by only 4 per cent. On physical examination, the patients having diffuse hemangiomas displayed three main findings—presence of a tumor (90 per cent), tenderness of the tumor (80 per cent), and discoloration of the skin over the tumor (60 per cent). On the other hand, 95 per cent of the patients having discrete tumors revealed pres-

ence of a tumor; 53 per cent had discoloration of the overlying skin and 47 per cent had local tenderness. Positive x-ray findings were present in 65 per cent of the diffuse cases and 44 per cent of the discrete. At the time of operation all of the diffuse hemangiomas revealed gross invasion of the adjacent tissues, while 23 per cent of the discrete tumors were invasive.

Pathologically, these tumors presented a bluish-red glistening appearance and on the cut section were not unlike a blood-filled sponge. The size of the diffuse tumors seemed to be practically unlimited, while the average size of the discrete tumors was 4.9 cubic centimeters. Microscopically, the picture of a mass of newly forming capillaries imbedded in sparse fibrous stroma characterized the capillary tumors, and the cavernous tumors consisted of numerous blood-filled spaces of varying degrees lined by flattened endothelium. A third type of microscopic picture was presented by a combination of these two basic types. Of the diffuse tumors, 15 per cent were purely capillary, 61 per cent were cavernous, and 24 per cent of these showed the combination of the two. On the basis of 8 microscopic characteristics the diffuse and the discrete tumors varied little.

The treatment afforded these 93 patients was surgical. Forty-six operative procedures were done in the 20 cases of diffuse tumors, of which 3 were amputations. Simple excision of the mass was carried out in all cases of discrete tumors. There were no operative deaths.

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HYSTERECTOMY IN YOUNG WOMEN

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IN THE PAST hysterectomy was considered a surgical procedure limited almost entirely to older women. However, the more advanced knowledge of physiology, pathology, and endocrinology, together with the increased safety of the operation, has broadened its scope so that now it is not too infrequently done in younger women, especially those in whom the nature of the pelvic disease has made future pregnancies impossible, or in whom the nature of the disease is the result of multiple pregnancies. In the younger group, this operation has replaced to some extent the partial and often very incomplete and "tinkering" surgical procedure heretofore practiced.

It is the purpose of the present article to review the hysterectomies done on women 30 years of age and younger from a clinical and pathologic standpoint. A study to evaluate the long-term results in these patients, both from a physical and psychologic standpoint, is now in progress (1).

MATERIALS AND METHODS

This study embraces hysterectomies performed in women, 30 years of age and younger, on the gynecological services of Baylor University College of Medicine and the Jefferson Davis Hospital, Houston, Texas, for the 30 month period, January 1, 1953 through June 30, 1955. All of these patients are ward cases and were operated on by the residents under the supervision of the attending staff.

The total number of hysterectomies performed during this period was 558. There were 395 total abdominal hysterectomies, 4 subtotal abdominal, and 159 vaginal (with and without repair). The number of hysterectomies done on women 30 years of age and younger during this stated period of time was 68, an incidence of 12.1 per cent. Table I shows the type hysterectomies performed in this younger age group. Sixty-five of these hysterectomies done in the younger age group were either total abdominal or vaginal. Only 3 subtotal hysterectomies were performed. Of the 3 subtotal hysterectomies performed, 1 was done for a spontaneous term rupture of the uterus on a patient in rather deep shock and not deemed a good surgical risk. One was done on a patient with extensive inflammatory disease, and the third on a patient with extensive endometriosis. In reviewing the charts of these latter 2 patients, it is believed that probably both of these could have had the total operation, but no criticism is directed, because of the nature of these conditions.

Age and color. The youngest patient in this series was 21 years old, and the oldest, of course, was 30. One patient was 21 years old, 3 were 22, 1 was 23, 4 were 24, 8 were 25, 9 were 26, 6 were 27, 12 were 28, 7 were 29, and 17 were 30 years old. It can be seen that the great majority were either 25 years of age or older.

Forty of these patients were colored and 28 were white. No significance is placed on this figure.

Parity. Parity ranged from 0 up to 9. There was a total of 192 pregnancies for these 68 patients, or an average of 2.9 pregnancies per patient. Twenty-two of this group were nulliparas, 8 were primiparas, 9 were para 2, 3 were para 3, 8 were para 4, 10 were para 5, 4 were para 6, 3 were para 8, 1 was para 9. Of the 22 patients who had never been pregnant, 20 were operated on

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TABLE I.—TYPE OF HYSTERECTOMY IN PATIENTS UNDER 30 YEARS OLD

		No. of cases
Total abdominal hysterectomy		45
With bilateral adnexectomy	20	
With unilateral adnexectomy	16	
Preservation both adnexae	9	
Vaginal hysterectomy		20
With anterior and posterior repair	14	
With repair	6	
Subtotal hysterectomy and bilateral adnexectomy		3
Total		68

for recurrent inflammatory disease, and 2 were operated on for large myomas.

Indications for surgery. Table II lists the indications for surgery. All patients with a diagnosis of carcinoma in situ had a fractional curettage and knife cone of the cervix with multiple sections, to rule out invasion before hysterectomy was resorted to. Of the 6 cases of carcinoma in situ, no invasion was found in the knife conization, and in the removed surgical specimen no evidence of the carcinoma in situ was found. This would indicate that perhaps a more conservative approach to carcinoma in situ in young women who wish to continue their childbearing capacity might be employed, as recommended by several authors. Before operating on these patients with carcinoma in situ, a conference was held with them, the disease process was explained to the best of our ability, and the final decision as to whether to resort to hysterectomy was then left to the patient. As all these patients were parous, all decided to have the hysterectomy.

Pathology. Table III shows the pathologic conditions encountered in these patients. Of the 23 cases in which histologic examination of a normal uterus was performed, 14 were done for uterine prolapse, cystocele, or rectocele. (One of these patients also had a preoperative diagnosis of carcinoma in situ.) Five of these hysterectomies were performed primarily for carcinoma in situ and, as stated previously, a fractional curettage and knife conization with multiple sections were done to rule out invasion before the hysterectomy was performed. Two patients in whom histologic examination of the uterus was performed were operated on for the pelvic fibrosis congestion syndrome, and 2 patients were operated on because of a fixed retroverted uterus with severe pelvic pain which failed to respond to the usual conservative measures. The two postpartum uteri listed in Table III represented the cases of spontaneous term rupture of the uterus and the elective cesarean section hysterectomy done for sterilization after the third section. Of the 3 cases listed as hemorrhagic ovarian cyst, type undetermined, in 2 a previous bilateral salpingectomy had been performed, and in the third evidence of a contralateral tubal occlusion due to inflammatory disease was present. The patient with a dermoid cyst had had a previous bilateral salpingectomy, and the patient with endometrial hyperplasia in the bicornuate uterus had congenital absence of both tubes.

Postoperative course. There were no deaths in this series. Fifty-six of these patients had an essentially uneventful postoperative course or, at the most, a low grade fever for 1 or 2 days only, not requiring any special therapy. Two patients developed cuff abscesses of the vagina which responded well to antibiotics and drained spontaneously. One patient developed a cuff hematoma which had to be evacuated on the fourth postoperative day. Two patients developed cul-de-sac abscesses, 1 of which drained spontaneously and 1 of which had to be incised. One patient developed a wound infection which was treated by antibiotics. One wound was allowed to heal by secondary intention. Two patients had mild respiratory infections, which responded well to the usual methods, and whether or not these patients had any underlying pulmonary infarction is not known, although it was suspected in both cases. Two patients had urinary retention beyond the expected time: both of these had vaginal hysterectomies with anterior and posterior repairs, and otherwise uneventful courses. Both were sent home with catheters in situ, and both had the catheters removed in 5 days with spontaneous voiding at that time. One patient upon whom vaginal hysterectomy was performed

exhibited signs of intraperitoneal hemorrhage on the second postoperative day and was reopened abdominally. A bleeding point in the right broad ligament was found and closed with a figure-of-eight suture. The patient made an uneventful recovery.

Follow-up. All of these patients were seen in the clinic anywhere from 6 to 8 weeks postoperatively, and at that time all of them reported marked relief from their symptoms. However, it is believed that such a short follow-up study is of very little value. At the present time, a study is in progress (1) to report on the long-term follow-up on these patients with regard to the following pertinent points: (1) long-term relief of symptoms following hysterectomy; (2) the psychologic effect of the inability to have future pregnancies and of the loss of menstrual function; (3) sex relations before and after surgery; and (4) the presence of vasomotor symptoms, the severity and type of treatment given, if any.

COMMENT

In this series of cases, 38 patients were operated on because of recurrent resistant pelvic inflammatory disease or symptomatic myomas. Our feeling about the pelvic inflammatory disease is that almost without exception these patients should either be treated by medical means or, when surgery is done, it should consist of a total hysterectomy and bilateral salpingo-oophorectomy. Unless it is possible to preserve some ovarian tissue with an adequate blood supply, it is best to clean out the pelvis and give the patient substitutional estrogen therapy, preferably by mouth. In the rare case in which there is an inflammatory mass limited to one adnexal region and the other tube is patent, unilateral salpingo-oophorectomy can be performed. It is in the realm of pelvic inflammatory disease that the incomplete and partial operations in the past, such as bilateral salpingectomy or partial removal of inflammatory masses, have yielded such discouraging results and only necessitated reoperating upon the patient at a later date.

TABLE II.—INDICATIONS FOR SURGERY (PREOPERATIVE DIAGNOSIS)

	No. of cases
Severe recurrent pelvic inflammatory disease	20
Symptomatic myomata	18
Prolapse or cystocele, rectocele	13
Carcinoma in situ (cervix)	5
Carcinoma in situ, plus prolapse, cystocele, rectocele	1
Persistent bleeding, previous bilateral salpingectomy	1
Pelvic congestion—fibrosis syndrome	2
Endometriosis	1
Spontaneous term rupture of uterus	1
Sterilization after third section	1
Ruptured ectopic, previous contralateral salpingectomy	2
Ovarian tumor, type unknown, previous contralateral salpingo-oophorectomy	1
Fixed retroverted uterus with severe pelvic pain	2

We believe that young women with symptomatic myomas can often be handled by a multiple myomectomy if both tubes are patent and other causes of infertility in either husband or wife do not exist or if myomectomy is impractical for technical reasons. In this series of cases, however, none of these patients was deemed suitable for myomectomy for the reasons already stated.

Fourteen patients had vaginal hysterectomies and anterior and posterior repair because of prolapse or cystocele or rectocele. We believe that vaginal hysterectomy and repair constitute the best treatment for this condition. If the patient desires more children, she is advised to complete her family and then have the operation performed. We very rarely resort to the Manchester procedure.

Six patients had carcinoma in situ and, as previously stated, no carcinoma in situ was found in the removed surgical specimen. All of these patients were treated by vaginal hysterectomy. Perhaps a more conservative

TABLE III.—PATHOLOGY

	No. of cases
Normal uterus (except for cervicitis)	23
Extensive pelvic inflammatory disease (uterus normal)	19
Pelvic inflammatory disease and myomata	6
Myomata only	5
Myomata and adenomyosis	2
Pelvic inflammatory disease and ectopic	4
Postpartum uterus	2
Hemorrhagic ovarian cyst (normal uterus)	3
Dermoid cyst (normal uterus)	1
Endometriosis, extensive (normal uterus)	1
Endometrial hyperplasia in bicornate uterus, congenital absence of both tubes	1

approach to carcinoma in situ of the cervix in young women might be used, but this is still a very controversial matter.

Two patients had ruptured ectopic pregnancies with previous contralateral salpingectomies. Since both were in good condition at the time of surgery, hysterectomy was performed. One patient had a dermoid cyst of the ovary with evidence of a previous bilateral salpingectomy. One patient had persistent bleeding with previous bilateral salpingectomy. We believe that in such cases as these, that is, the patient in whom a pelvic laparotomy is being done and it is found that future pregnancies are impossible because of previous removal or bilateral occlusion of the tubes, the uterus should be removed at the time of laparotomy, provided the patient is in good shape and has been informed of such possibility beforehand.

The 2 cases of pelvic congestion syndrome and the 2 cases of extreme pelvic pain with retroverted uterus deserve some comment. The former 2 patients had had 4 pregnancies each, and the latter 2 had had 2 pregnancies each. Taylor (2, 3, 4) has written extensively about the pelvic congestion fibrosis syndrome and emphasizes emotional factors as a major cause. As yet, the management of these cases is not clear, and whether or not to proceed with a hysterectomy must be approached with extreme caution, since it is possible that surgery may not only fail to relieve the symptoms but may even make them worse. Surgery should be done only after failure of all conservative measures and after a very exhaustive evaluation of emotional factors. We hope that a prolonged follow-up on this type of case may throw some light on this very perplexing problem.

In conclusion, then, we wish to state that it is not our intention to give the impression that hysterectomy is the treatment of choice for all young women with pelvic complaints. However, to some extent, this procedure has replaced the partial and, often incomplete, surgery which has been done in the past on such women and which has yielded such discouraging results. We hope that the study in progress with regard to the long-term follow-up on these women will give us some clue as to whether or not we are proceeding along the right lines.

SUMMARY

1. A review of hysterectomies performed upon women 30 years of age and younger on a large university service is presented from the clinical and pathological standpoints.

2. The indications for performing hysterectomy on such patients is discussed.

3. A long-term follow-up on these patients is now in progress to evaluate the final results from a physical and psychologic standpoint.

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AN EXPERIMENTAL STUDY OF INTRAHEPATIC DISTRIBUTION OF PORTAL BLOOD

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IN 1901, SEREGE performed a series of experiments on animals the results of which suggested the presence of selective distribution of portal blood within the liver. As yet, conclusive proof that venous blood from specific abdominal organs drains to a particular portion of the liver has not been forthcoming. Many conflicting reports either substantiating or opposing Serege's theory have appeared in the literature. This unsettled issue was of sufficient interest to us to warrant further examination, using a more precise technique of measuring the distribution of portal blood within the liver. The physical properties of the indicators used in the earlier experiments and the experimental design of many, necessitating considerable manipulation of the liver and portal bed, are two objections of the methodology employed by previous investigators. By using radioactive isotopes and scintillation counting techniques, it is possible to determine the distribution of the portal blood within the liver objectively and at the same time avoid displacement of the liver or distortion of the portal bed.

METHOD

Healthy mongrel dogs were used in all experiments. They were anesthetized with intravenous nembutal, 0.5 milliliter per kilogram of body weight. The abdominal cavity was opened through a midline incision. Scintillation counters were then placed in contact with the external body wall directly over the right and left lobes of the liver under direct vision. Each scintillation counter was connected to a counting rate meter, and the two meters were connected to a dual channel potentiometric recording instrument. Ten to 25 microcuries of radioactive iodine labelled rose bengal dye dissolved in approximately 2 milliliters of normal saline were injected into the smallest possible venous radicle draining the organ being studied. It was injected over a period of 15 seconds. During the injection care was exercised to avoid unnecessary traction on the venous system or significant displacement of the abdominal viscera. At the start of the injection "zero time" was indicated on the recording graph paper. Subsequent changes in counting rate due to variable amounts of activity registered by the counters were simultaneously recorded as a function of time. These data were replotted on ordinary graph paper with the counting rates expressed as a per cent of corrected peak count versus time.

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This study was conducted in part with facilities made available through contract No. W-31-109-ENG-78 between the United States Atomic Energy Commission and Western Reserve University.

RESULTS

A total of 12 experiments were performed representing four different areas of the portal venous system: small intestine, spleen, cecum, and left colon. In all instances a prompt rise in radioactivity over the right and left portions of the liver was noted following injection of the radioactive iodine labelled rose bengal irrespective of the site of injection. The time at which peak radioactivity was detected in the right and left side of the liver varied only slightly and in several instances was identical (Fig. 1). Likewise, the corrected peak counts obtained from the counting rate meters for the two

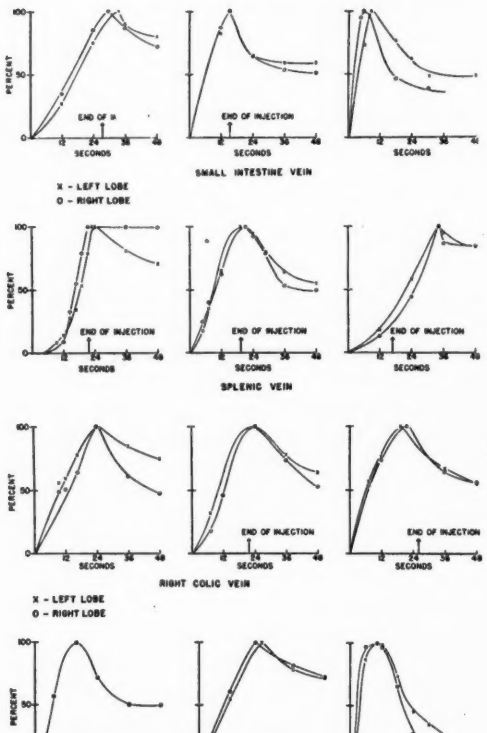

FIG. 1. Experiments with data plotted as percentage of peak counts of radioactivity against time.

sides showed some variation in radioactivity but no consistent preponderance in activity was seen for either side of the liver (Table I).

DISCUSSION

In the light of these findings it seems unlikely that venous blood from a particular portion of the portal bed is destined to be transported to a specific area within the liver parenchyma. In order for this situation to occur it would require "laminar" or "streamlined" flow within the portal vein, a phenomenon which Copher maintains exists. There is little doubt but that a certain degree of laminar flow may be manifest in experiments involving the injection of material into the portal stream which is not freely

TABLE I.—CORRECTED PEAK COUNTS OF RADIOACTIVITY INJECTION OF I^{131} ROSE BENGAL

Site of injection		*Right lobe*	*Left lobe*
Small intestine vein.....	1.	46,000	40,000
	2.	45,000	45,000
	3.	62,000	55,000
Splenic vein.....	1.	52,000	58,000
	2.	75,000	80,000
	3.	70,000	78,000
Right colic vein.....	1.	47,000	32,000
	2.	81,000	22,000
	3.	74,000	51,000
	4.	7,000	7,000
Left colic vein.....	1.	31,200	13,000
	2.	30,000	61,000

miscible with blood or in areas in which the rather rapid axial flow at the site of injection does not permit homogenization. However, when the physical properties of the indicator allow easy mixing with blood and when it is injected into the smallest peripheral vein possible, the indicator will be presented to the liver homogenized with other soluble elements of the blood. The sluggish flow in small venous radicles and the turbulence created by the ingress of small tributaries along the course of the portal bed give credence to this line of reasoning which was borne out by our experimental data. Furthermore, in the absence of any known morphologic, histologic, or cytochemical differences between various lobes of the liver it seems implausible to assign the lobes different biologic functions in view of present knowledge.

SUMMARY

Using radioactive iodine labelled rose bengal as an indicator and scintillation counters to detect intrahepatic distribution of the dye, so significant differences were noted in the amount of dye or the rate at which peak values were attained between the right and left sides of the liver when the radioactive dye was delivered to the lobes from four different sites in the portal bed.

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THE INFLUENCE OF HORMONE THERAPY ON METASTATIC MAMMARY CARCINOMA

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THE EVALUATION of the beneficial effects of any form of therapy on advanced carcinoma of the breast can be determined only by a detailed comparative study using the natural history of the disease as the basic standard of comparison. The most complete study of the course and average survival of untreated cancer of the breast was reported in 1951 by Shimkin (6). The average 5 year survival from the onset of disease was 20 per cent.

The mean duration of disease of untreated mammary carcinoma is included in Table I. Greenwood reports a mean duration of disease of 38 months in 651 cases.

The published reports to date on the average course of recurrent carcinoma of the breast after previous control of primary carcinoma are not as conclusive, as in the reports to date the results have been partially influenced by some form of therapy for the metastases. Shimkin (7), in 1954, published a very detailed statistical analysis of recurrent breast cancer. In Table II is presented the material recorded in that survey. It represents a study of 1,066 cases of recurrent breast cancer. This table demonstrates the comparative intervals during the course of the disease of treated carcinoma of the breast. The three time intervals, onset of disease to initial control, control to recurrence, and recurrence to death, can be represented on an average by a ratio of 1 to 2 to 1. One concludes that the average interval from recurrence to death in treated carcinoma of the breast is approximately one-quarter of the total survival time from the onset of the disease. Applying this calculation to the average survival of untreated cancer of the breast, i.e., 38 months, the average survival, from the clinical evidence of generalized dissemination to death, is estimated to be 9.5 months.

Stoll and Ellis, in 1953, reported an average survival of 3.7 months following untreated pulmonary metastases. Shimkin (7), in 1954, reported an average survival much longer following the development of local and osseous metastases than in the case of generalized disease. In his series of 374 cases, the average survival is shown in Table III. These survival figures do not apply entirely to untreated recurrent cancer of the breast, as approximately 50 per cent of the total received treatment, chiefly by irradiation (for osseous and local metastases).

The overall average figure of 17.6 months is comparable to the estimated average survival in our own experience, as shown in Table IV which demonstrates the comparison of survivals of untreated and irradiated cases of recurrent breast carcinoma. Two hundred eighty-six cases of recurrent carcinoma of the breast during the years 1933 to 1938 were observed in the Department of Radiotherapy, Toronto General Hospital. Of 106 cases of untreated recurrent carcinoma of the breast, the average survival after the first clinical evidence of recurrence was 7.8 months. By combining the irradiated and the nonirradiated, the average survival was 18.1 months. During the same years there were also 80 patients who had clinical evidence of generalized metastases when first recognized, and who died within 3 months. This latter group was excluded from the survival estimations in order to ensure a stricter comparison between the treated and untreated initial recurrences.

Having established the basic measures for comparison, the response to hormone ther-

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TABLE I.—NATURAL HISTORY OF UNTREATED CANCER

Site	*No. of cases*	*Mean age at onset, yrs.*	*Mean duration of disease, mos.*
Breast	651	57	38
Rectum	887	55	27
Cervix	1,749	48	21
Oral cavity	369	57	17
Stomach	154	52	17
Larynx	129	52	15
Esophagus	299	55	12

After Greenwood, 1926.

apy can be more correctly assessed. A summary of the figures to be kept in mind in evaluating any response to treatment for carcinoma of the breast follows: According to the Shimkin (6) series the 5 year survival rate was 20 per cent; Greenwood reports a mean total survival period of 38 months; the mean survival period—recurrence to death—in the present series was 7.8 months.

When dealing with large numbers of patients, one observes the occasional dramatic response to hormone therapy, but one's enthusiasm is dampened by a succession of poor responses. However, it is a satisfaction to the physician, and a comfort to the patient, when more time-tested methods have failed, to be able to suggest hormonal control. Ignoring completely the statistical results, the gratification from observing the comparatively few excellent results makes the treatment worth while for all who are eligible.

In our Institute, 330 patients have received an adequate trial of either androgen or estrogen, or both, since 1940: 282 patients were treated with androgen, 83 with estrogen, and 35 received a trial of both hormones. The androgen most commonly employed was testosterone propionate in oil, giving 150 milligrams intramuscularly twice weekly over a period of 10 weeks, dropping the dosage to 100 milligrams weekly if the treatment was continued longer. As an alternative, testosterone linguets, 10 milligrams three times daily were prescribed in the minority of the entire group so treated. Those receiving estrogen therapy were given 3 to 5 milligrams three times daily, stilbestrol, or a synthetic substitute of comparable dosage for varying periods of time, depending on the patient's tolerance.

In this survey, 35 of the 330 patients received a trial of both androgen and estrogen, making a total of 365 responses to hormone for study. The survival recorded as the response to one type of hormone therapy is the interval in months from the institution of that course of treatment until changed to either the opposite hormone, to cortisone therapy, to bilateral adrenalectomy, to pituitary irradiation, to extensive radiotherapy, or to death if no other form of radical treatment had been used. There are two minor exceptions to this rule, which I believe have had no appreciable effect on the recorded survivals, but have created a minor treatment overlap in a few instances. Firstly, included in the younger age group are a few patients who were castrated by irradiation in conjunction with testosterone therapy. Secondly, a small number of patients are included who received minimal irradiation for a specific reason, such as preventing breakdown of an impending ulceration, or attempting to ward off collapse of a vertebra, but all in this category had multiple sites of involvement; consequently, the irradiation

TABLE II.—MEAN SURVIVALS IN MONTHS OF PATIENTS WITH CANCER OF THE BREAST, WITH SUBSEQUENT RECURRENCE TERMINATING IN DEATH

	Onset to operation	*Operation to recurrence*	*Recurrence to death*	*Operation to death*	*Onset to death*
SERIES 2					
Stage I	10 (333)	43	19 (34)	62 (75)	72
Stage II	13 (296)	26	14 (90)	40 (157)	53
Stage III	18 (310)	16	13 (73)	28 (140)	46
SERIES 1					
Recurrent	12 (127)	35	19 (177)	54 (237)	66

Numbers in parentheses refer to number of cases on which means are based.
After Shimkin (7), January 1954.

received would not have altered the course of the disease.

The criteria for initiating hormone therapy in this series were as follows: (1) clinical evidence of generalized metastases; (2) clinical evidence of metastases involving a single site not amenable to radiotherapy, i.e., lung or liver; (3) progression of metastases amenable to radiotherapy after the tolerance to radiotherapy has been exhausted; (It has previously been established that irradiation offers good palliation to localized radiosensitive disease in the absence of generalized dissemination. Thus we still irradiate whenever possible and reserve hormone therapy for a later exacerbation.) (4) advanced primary disease not previously treated by any recognized method, with multiple areas of involvement beyond the operative site.

Keeping in mind the average figures related to the natural history of the disease, the influence of hormone therapy on the 5 year survival in this series is first estimated. Of 330 patients, 100 survived for over 5 years giving a survival rate to date of 30 per cent. In 40 of these patients, hormone therapy was instituted less than 5 years after initial control. The 5 year survival of 30 per cent, as opposed to 20 per cent in untreated cancer of the breast, is calculated from the beginning of treatment and does not include the interval between the first clinical evidence of disease and the initial control, which on an average is calculated to be one-quarter of the total span of the disease. Thus a 30 per cent 5 year survival is a modest figure as opposed to 20 per cent of the so-called "untreated." One also is mindful of the fact that this series of cases does not include any of successfully treated early cases, which are apparent "cures" or which have remained controlled for many years. On close examination, one finds that 40 of the 100 who survived 5 years or more received hormone therapy at various intervals prior to reaching the "5 year mark." Thus, hormone treatment could conceivably have been the controlling factor which prolonged the survival of this group of 40 to add a possible 12 per cent to the 5 year survival percentage. The average survival for the entire group after the institution of hormone therapy was 12.1 months, and after the onset of first recurrences was 19.3 months, which is an improvement of 11.5 months over untreated recurrences.

TABLE III.—SURVIVAL AFTER RECURRENCE BY TYPE OF RECURRENCE IN SHIMKIN SERIES

	No. cases	*Mean survival, mos.*
Local	98	28.4
Osseous	83	22.6
Generalized	193	10.0
Total	374	17.6

After Shimkin (7), 1954.

Included in this series, as shown in Table V, are 4 cases for which hormone therapy was the only method of treatment for primary or secondary disease, and 60 patients who received this treatment alone for recurrences, the primary having previously been treated by surgery. The percentage improved by hormone treatment in the latter group is higher than in any other selection of cases in this series and the average survival is slightly longer. Thus, previous radiotherapy may prove to be a factor which helps to preclude a good response.

Before disposing of generalities with reference to this survey, the incidence of subsequent endocrine controls is outlined as follows: On exacerbation of the disease during any one type of hormone therapy, in addition to the 35 patients who were changed to the opposite hormone, 5 patients later were treated by cortisone therapy (4 with remarkable improvement), 19 had a bilateral adrenalectomy, performed by Dr. Norman C. Delarue, Surgical Consultant for Breast Carcinoma to the Department of Radiotherapy, and 3 received pituitary irradiation (2 with improvement).

TABLE IV.—AVERAGE SURVIVAL AFTER INITIAL RECURRENCE AT TORONTO GENERAL HOSPITAL, 1933 TO 1938

	No. cases	*Average survival, mos.*
Recurrent irradiated	180	24.7
Recurrent untreated	106	7.8
Total	286	18.1

TABLE V.—NO TREATMENT EXCEPT HORMONE THERAPY

	No. of cases	*Survival, mos.*
For primary or secondary disease		
Stilbestrol	2	24
Testosterone	2	1
Total	4	
For metastases only		
Improved	40	18.8
Unimproved	20	4
Total	60	13.9

A few writers, particularly Huggins, have stressed the importance of the pathologic type in the response to hormone control, claiming that adenocarcinoma of the breast offers the best prognosis. Table VI presents a summary of the hormone responses according to the pathologic type when specified. With the exception of scirrhous carcinoma, the total number in each group is not sufficiently large to draw any conclusions.

Of prime importance is the comparison of the response to androgen as opposed to estrogen therapy. The subjective response was assessed entirely by the periodic reports from the patient. The objective response was more difficult to determine. In this series the decision to regard the response as positive is based on: (1) verification of improvement by comparison of radiographs prior and subsequent to an adequate course of hormone; (2) clinical observations on disease which can be palpated or visualized; and (3) a period of quiescence during the course of therapy, as opposed to a rapid progression of the disease prior to the institution of hormone treatment.

The subjective and objective responses to both hormones are summated in Table VII. One notes that in each case there is an intermediary group listed as subjective response positive and objective response negative. These cases showed a gradual progression of disease. But the subjective improvement and the slackened speed of progression suggested that the hormone had had a retarding effect. Perhaps, in the near future, it will be possible to demonstrate this retarding process by means of biochemical and metabolic studies, as well as histologic and cytologic studies, making the objective response more definite. This intermediary group has been included among the improved or satisfactory palliations in all succeeding comparisons.

TABLE VI.—INFLUENCE OF PATHOLOGIC TYPE ON RESPONSE TO HORMONE THERAPY

Pathology	*Good response No. cases*	*Poor response No. cases*
Scirrhous	38	32
Anaplastic	2	2
Medullary	8	5
Duct ca.	6	7
Adenocarcinoma	7	4
Carcinoma	104	115
Total	165	165

This table demonstrates that the poor responses to testosterone outweigh the satisfactory responses. The reverse is true in the estrogen group, the total number of successes exceeding the total failures. Then by combining the successes of both androgen and estrogen, the overall total number of successes represents exactly one-half the total number. Using percentages of the total in each group, instead of total number of cases, one notes a 30 per cent definite objective response to testosterone and 42 per cent to estrogen.

Observing the better results from estrogen therapy, one immediately wonders whether this is a direct result of the age group concerned, or whether it is due to a difference in the biologic response. Table VIII demonstrates the age group distribution according to the menopause of those receiving estrogen and androgen therapy. As we have so far rarely prescribed estrogens in the younger age group, the response to testosterone in the postmenopausal age group is comparable to the response to estrogen. In the menopausal group and younger group, the number of poor responses to testosterone markedly exceeds the number of satisfactory responses.

The response to both hormones is combined in Table IX with reference to age group. This table shows that a satisfactory response can be expected in only 2 out of every 5 patients in the menopausal and premenopausal age groups, but in the postmenopausal group a good response can be anticipated in 3 out of every 5 patients.

Closely related to the age influence is the influence of an induced menopause on the

TABLE VII.—RESPONSE TO HORMONE THERAPY IN MAMMARY CANCER

		Cases		Satisfactory palliation		
S	*O*	*No.*	*Per cent*	*No.*	*Per cent*	*Total*
		ANDROGEN				
+	+	85	30			
+	—	48	17	133	47	
—	—	149	53			282
		ESTROGEN				
+	+	35	42			
+	—	15	18	50	60	
—	—	33	40			83
Total.....				183	50	365

S, subjective.
O, objective.
+, improved.
—, reactivation.

TABLE VIII.—RESPONSE TO HORMONE THERAPY, DISTRIBUTION BY AGE GROUP INCIDENCE

Age group	*Satisfactory response, No.*	*Poor response, No.*
	ESTROGEN—83 CASES	
Pre.....	0	1
Conc.....	2	4
Post.....	48	28
Total.....	50	33
	ANDROGEN—282 CASES	
Pre.....	38	52
Conc.....	34	51
Post	61	46
Total.....	133	149

Pre., premenopausal age group.
Conc., concurrent with or within 5 years after menopause.
Post., at least 5 years after menopause and older.

response to hormone therapy. In this series the majority of castrations were by irradiation. Table X presents the percentage of the total number of hormone treated patients who also received a course of irradiation directed to the ovaries, adequate to cause a partial castration and, in the younger age group, sufficient to cause a cessation of menstruation. It was rather surprising to find that 50 per cent of the entire group were so treated. If this procedure was carried out several months prior to the institution of hormone therapy, it was usually a part of the prescribed course of radiotherapy for osseous metastases. According to this table, castration does not seem to have altered the response in general to testosterone.

But, while recording the data for this survey from the original histories, I was impressed by the number of poor responses to testosterone when the castration irradiation was administered concurrently with the institution of the course of testosterone. Consequently, the influence of the interval between castration and hormone therapy was studied, and the final count as shown in Table X did demonstrate that the majority of poor responses to testosterone was coincident with castration. Of 53 cases showing a poor response to testosterone, 39, or 74 per cent, were castrated at the same time as or within 3 months prior to the course of testosterone. In endeavoring to interpret this finding one wonders whether it is associated with some unknown antagonistic response. But it does reinforce the more recent theory that testosterone therapy has a much different biologic effect than castration and on this basis alone these two treatment measures should not be carried out concurrently. For instance, there is included in this survey 1 case of the premenopausal age group which responded very poorly to castration resulting from irradiation to the pelvis for osseous metastases after a 2 year objective remission following testosterone therapy. Pearson and associates report a 44 per cent objective remission by surgical castration, which is a higher percentage than by testosterone therapy in the younger age groups unless the subjective response is considered in conjunction with it. But the average duration of the remission, 9 months, as reported by Pearson, is not as long as the average duration of remission to testosterone therapy, which, in this series, is 12 months.

Considering the slight variation in the response to these two methods of palliation, I do not believe that it is yet justified to prescribe the irreversible procedure when it is

TABLE IX.—RESPONSE TO HORMONE THERAPY VERSUS AGE GROUP WITH RELATION TO MENOPAUSE

Age group	*Satisfactory palliation*		*Poor response*		*Total*
	No.	*Per cent*	*No.*	*Per cent*	
Pre.....	38	42	53	58	91
Conc.....	36	40	55	60	91
Post.....	109	59	74	41	183
Total.....	183	50	182	50	365

Pre., premenopausal age group.
Conc., concurrent with or within 5 years after menopause.
Post., at least 5 years after menopause and older.

TABLE X.—INFLUENCE OF INDUCED MENOPAUSE AND INTERVAL BETWEEN ANDROGEN THERAPY AND CASTRATION ON RESPONSE TO ANDROGEN THERAPY IN PREMENOPAUSAL AND CONCURRENT AGE GROUPS

	Response			
	Satisfactory		*Poor*	
	No.	*Per cent*	*No.*	*Per cent*
Androgen therapy	74		108	
Plus irradiation or surgery	37	50	53	49
3 mos. pre. or post. androgen	19	25	14	13
Same time as androgen	18	24	39	36

90, or 49.5 per cent, of 182 hormone treated patients received irradiation castration also.

TABLE XI.—RESPONSE TO HORMONE THERAPY, AVERAGE SURVIVAL IN MONTHS BY SITE OF METASTASIS PREDOMINATING

	Satisfactory		*Poor*	
Site of metastasis	*No.*	*Av. surv., mos.*	*No.*	*Av. surv., mos.*
	ANDROGEN			
Osseous	50	17.1	53	4.6
Lung	35	16	42	4.5
Soft tissue	35	16.7	28	5.3
Generalized	13	13.5	26	3.1
Total	133		149	
	ESTROGEN			
Osseous	8	20.5	8	4.5
Lung	15	22.3	8	3.8
Soft tissue	19	13.4	7	3.4
Generalized	8	14.5	10	2.3
Total	50		33	

possible to test the response by following a method of treatment which may be observed in its effects and reversed if necessary to the advantage of the patient. A study of the cases in which both hormones have been used bears out this conclusion. These facts will be presented later in this article.

The response to hormone therapy on the various sites of involvement has been reported by a few authors recently. Nathanson, in the July 1952 issue of *Cancer*, reporting on 253 cases treated by estrogen and 105 cases by androgen, noted a much more effective response to estrogen therapy in controlling soft tissue and lung metastases, but found the two steroids equally effective in controlling osseous metastases. Table XI is very detailed, but one may conclude from it that our results agree with those of Nathanson regarding osseous metastases, but that the response is much more prolonged from estrogen. This table shows a higher percentage response in lung metastases by estrogen, and as well a more prolonged effect than by testosterone. In soft tissue recurrences, a higher percentage response to estrogen therapy is shown, but a more prolonged effect is obtained by testosterone.

In the collected data, as reported in the *Journal of the American Medical Association* (1), June 1951, on the current status of hormone therapy, 441 cases treated by testosterone were reported as having a mean survival of 8.5 months. Our series shows a corresponding figure of 10.0 months. The average survival following the institution of estrogen therapy in the same publication was reported as 9.8 months. In our series the comparable mean survival was 11.5 months.

The final relationship is the influence of the interval between intitial control and onset of recurrent disease on the subsequent control by hormones. Our experience in this respect is demonstrated in Table XII. The results are definitely significant. The poorest response to hormone therapy appears in the patients whose recurrences appeared less than 2 years after the initial control. The best response is noted when the interval to recurrence was between 2 to 5 years, indicating a better host resistance. This resist-

TABLE XII.—RELATION BETWEEN INTERVAL TO RECURRENCE AND SURVIVAL FOLLOWING HORMONE THERAPY

	Response to Hormone Therapy							
	Satisfactory				*Unsatisfactory*			
Interval control to recurrence	*No. of cases*	*0–12 mos.*	*13 mos.+*	*Average survival, mos.*	*No. of cases*	*0–12 mos.*	*13 mos.+*	*Average survival, mos.*
Under 2 yrs.	56	26	30	16.6	85	85	0	5.3
2–5 years	49	15	34	21.0	30	30	0	7.0
Over 5 yrs.	20	5	15	20.3	22	21	1	11.9
Not stated	6	2	4	14.7	2	2	0	1.0
Advanced primary, no prev. surgery	34	19	15	13.7	26	26	0	5.3
Total	165	67	98	17.7	165	164	1	6.4

ance seems to wane when the interval between initial control and recurrence extends beyond a 5 year period, as shown by the response.

Table XII also demonstrates the comparatively poor response to hormone therapy in the groups of primary inoperable carcinoma of the breast with metastases, the average survival following hormone therapy being of a much shorter duration than all of the other categories which are demonstrated in this table.

Before concluding, the 35 patients receiving a trial of both hormones deserve special mention since the study of this group is enlightening as well as in line with previous observations. Five (14 per cent) of these patients showed a good response to both hormones; 8 (23 per cent) showed a poor response to both; 15 (43 per cent) showed a good response to estrogen only; and 7 (20 per cent) showed a good response to androgen only. Since only 23 per cent showed no response to either androgen or estrogen, some response to either hormone can be expected in 77 per cent of the total number. The explanation for the favorable response to both hormones in 14 per cent of the total is obscure, but probably could be explained by a physiologic response unrelated to hormone dependence. Until recently, we have been hesitant about prescribing estrogen therapy in the menopausal group, after the response to testosterone has been a failure. But these results, combined with our observations on a few dramatic responses to estrogen in this age group, have reinforced our opinion that a trial of estrogen should be considered, in spite of the age of the patient, when testosterone fails.

From clinical observations only, I am becoming more and more convinced that exacerbations after instituting hormone therapy can often be detected within 2 weeks, and that it is not always necessary to continue the use of one hormone for at least 2 months, thereby reducing the prospect of control by other hormones or other more radical measures.

SUMMARY AND CONCLUSIONS

In summarizing, the following conclusions may be drawn from this survey and in the main are supported by the results of similar studies:

1. The introduction of hormone therapy appears to have appreciably prolonged the survival of cases developing metastatic mammary carcinoma, as compared with untreated carcinoma of the breast.

2. A more successful response to hormone therapy for metastatic disease was noted when no previous treatment had been undertaken.

3. The pathologic type of mammary carcinoma has not appreciably influenced the response to steroid therapy in this series.

4. The response to estrogen in this series has been more satisfactory than the response to androgen, both in percentage responses and in length of remissions.

5. In the older age group only, the response to testosterone therapy is equally as satisfactory as the response to estrogen. Only 2 of every 5 patients in the premenopause and menopause age group respond to testosterone.

6. Previously induced menopause does not seem to have altered the response to testosterone therapy, but a castration by irradiation concurrent with testosterone therapy was successful in only a small minority so treated.

7. It is suggested that the response to testosterone should be tested before advising a permanent castration.

8. For osseous metastases testosterone is equally as effective as stilbestrol, but the response to estrogen is more prolonged.

9. Estrogen is shown to effect a better palliation than androgen for lung metastases.

10. For soft tissue metastases, estrogen effects a higher percentage response, but the response to testosterone, when effective, is more lasting.

11. For generalized disease, estrogen showed a higher percentage response rate, but there was no appreciable difference in the length of remissions from either hormone.

12. In this series the mean survival following testosterone therapy was 10.0 months, and subsequent to estrogen therapy was 11.5 months.

13. A better response to hormone treatment can be anticipated if the interval between the initial control of the primary and onset of recurrence is over 2 years and under 5 years.

14. A poor response to hormone therapy is expected in the presence of primary inoperable breast cancer as well as metastatic disease.

15. A study of the patients receiving a trial of the antagonistic hormones reveals the possibility that approximately 77 per cent would respond to either of the hormones. There is sufficient evidence to suggest that estrogen therapy should be attempted in the younger age groups if a short trial of testosterone therapy produces an exacerbation of the disease.

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THE EFFECT OF ACUTE POTASSIUM DEPLETION ON THE FUNCTIONAL COMPARTMENTALIZATION OF WATER

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STATES OF HYPOKALEMIA or diminished total exchangeable potassium are often associated with hypotension of an intractable sort. Clinically, one observes a good response to transfusion or infusion over a relatively short period of time, followed by a return of the blood pressure to its previously low level.

It must be recognized that such patients have a great deal the matter with them aside from a loss of total exchangeable potassium, and the association of a hypotensive tendency with this particular facet of the patient's problem may be purely fortuitous. This characteristic of the depleted patient has been remarked upon by many, and has been named "chronic shock" by Clark and associates. They have recorded their conviction that the cause is a deficiency of blood volume. The present article presents data which suggest that potassium deficiency is an important element in the etiology of the syndrome, and that the plasma volume per se (and blood volume) is not diminished.

It appeared that one method of studying this clinical phenomenon might be by the removal of this predominantly intracellular ion (K^+), with substitution for it within the cell of one ordinarily largely extracellular (Na^+) in position. Acute depletion of potassium in dogs has been achieved through the use of the Kolff-Brigham artificial kidney, as outlined later. The effect on deuterium oxide (D_2O) equilibration curves, and on the dynamics of fluid compartmentalization are quite definite. Both the results and their significance will be discussed.

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METHODOLOGY

Because of their better tolerance of the hypotension which was observed to accompany the initiation of dialysis, large dogs were selected for these studies, weighing no less than 12 kilograms. A preliminary determination of the total exchangeable potassium was done on some of these animals by the isotope technique of Corsa and associates, employing the urinary specific activities for the necessary calculation. It should be noted parenthetically that these radioactive potassium studies showed interesting postequilibration differences in the specific activities of muscle, plasma, and urine which will be reported elsewhere (10). We have employed the urine data here because previous estimates of the total exchangeable potassium (K_e) expressed in milliequivalents per kilogram of body weight have been based on urine specific activities.

Six weeks after this determination of total exchangeable potassium, control determinations of the Evans blue, sucrose, and D_2O volumes of distribution were done according to our previously developed techniques (8, 9, 13). The only additional procedure consisted of the determination of the rate characteristics of the curve of D_2O equilibration into its volume of distribution. The frequent and rapid sampling necessary for this technique was made possible by cannulation of the superficial femoral artery until the tip of a polyethylene tube lay in the aorta. The tube was then fixed in place with a silk tie and clamped with a rubber-shod hemostat. A zero time (Bo) sample (3 ml.) was drawn by insertion of the poly-

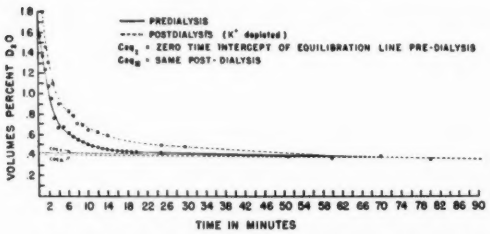

FIG. 1. Dog 1-D. D_2O equilibration curves before and after dialyses, exhibiting the marked differences characteristically induced by K^+ depletion.

ethylene tube into a glass ampule. Thereafter, 2 pulses of blood were allowed to escape prior to collection of each succeeding specimen. The jugular vein was now entered with a No. 20 gauge needle attached to a calibrated syringe, and 20 milliliters of 99.8 per cent D_2O given as rapidly as possible. A stop watch was started when the plunger reached the 10 milliliter mark. This needle was withdrawn as soon as the injection was complete. Samples were then taken in the ampules every minute to 15 minutes, every 10 minutes to 50 minutes, every 3 minutes to 71 minutes, and then every 20 minutes to 130 minutes. The ampules were sealed as soon as possible after the samples were procured, and stored at 4 degrees C. until ready for analysis.

The determination of the concentration of D_2O was carried out according to the densimetric method described by Schloerb and associates. The concentrations were calculated for each sample, and then plotted against time on arithmetic graph paper. These plots gave curves similar to that seen in Figure 1. The multiexponential equilibration curves were then analyzed by successive subtraction of components. It was found that there were only three distinct and readily determinable components which could be distinguished: (1) the constant equilibration (C_{eq}) component, the slope of which represents primarily urinary loss following complete equilibration, (2) "slow" equilibration component (K_2), presumably representing equilibration into cellular water, and (3) the "fast" equilibration component (K_1), presumably representing equilibration into the extracellular fluid. There was also an inconstant faster component which could represent a more rapidly equilibrating component of the extracellular water or a mixing factor or both. Because of its inconstant presence, it has not been shown as a separate phase of the curve.

The graphic technique employed was as follows: The fitted C_{eq} component (Fig. 1) was subtracted from all concentrations prior to the establishment of equilibration and the results plotted on semilogarithmic paper with time as the horizontal co-ordinate. The usual judgment was then made on the time of bending of the curve, and all points subsequent to this inflection fitted by the method of least squares. This fitting of the points to their best linear representation gives us the slope (K_2) of this component, its zero time intercept (C_1); and its "point of concentration extinction," set here at the level of .001 volume per cent above the concentration level of the C_{eq} line. The time coordinate of this point is designated t_2.

From the equation so calculated, the concentration contribution of this component of the curve is now calculated for each time for which a sample is available prior to the time (t_2). These concentrations are subtracted from those remaining prior to t_2 in Figure 2.

These calculated points are now plotted, examined for linearity, and fitted by least squares to obtain the zero intercept (C''), slope (K_1), and time of extinction (t_1), of the first component of the curve. t_1 is defined in the same way as t_2 except that t_1 refers to the steeper component of the curve. These characteristics of the curve components are shown graphically in Figure 2.

As indicated, it was not possible to separate a fourth component with consistency, although in some of the curves it was evident that an even more rapid component was present in the first 3 to 4 minutes. The variation in K_1 introduced by this rapid component was found to be slight even when clearly present.

After this procedure, 6 weeks were allowed to pass before further work was done on the dog. The passage of this length of time was sufficient for a return to normal in the plasma hemoglobin, red blood counts, and weights.

The dogs were then dialyzed on the artificial kidney against a normal bath or a potassium-free one, depending on the experimental requirements.

ARTIFICIAL KIDNEY PROCEDURE

On the day preceding the dialysis, the dogs were lightly anesthetized and their femoral vessels isolated for a distance of approximately 6 centimeters through a wide transverse groin incision. In this manner troublesome oozing from the operative area, due to the deliberately high degree of heparinization made necessary by dialysis, was avoided. At this time, 3 donor dogs were bled, collecting approximately 300 milliliters from each in heparinized bottles. This blood was cross-matched with that of the subject animal, and stored at 4 degrees C. overnight. In addition, plasma sodium, potassium, and bicarbonate concentrations were determined on the donor's and recipient's plasma.

The following morning the animal was placed in the dorsal decubitus beside the Kolff-Brigham artificial kidney (described by Murphy and associates), given sodium pentobarbitol anesthesia, and the tygon cannulas leading to the inflow and outflow tubes placed in the femoral artery and vein, respectively. At this time, the wound made the preceding afternoon was dry. Previously outlined techniques for the use of this apparatus were followed. Approximately 90 feet of previously boiled seamless cellophane tubing 23/32 inch in diameter, served as the dialyzing membrane. Small bore polyvinyl tubing was shaped into arterial and venous cannulas, and this same tubing used as conduits to and from the cellophane membrane. The entire extracorporeal system was primed with a measured quantity of the cross-matched blood (about 500 c.c.). Each

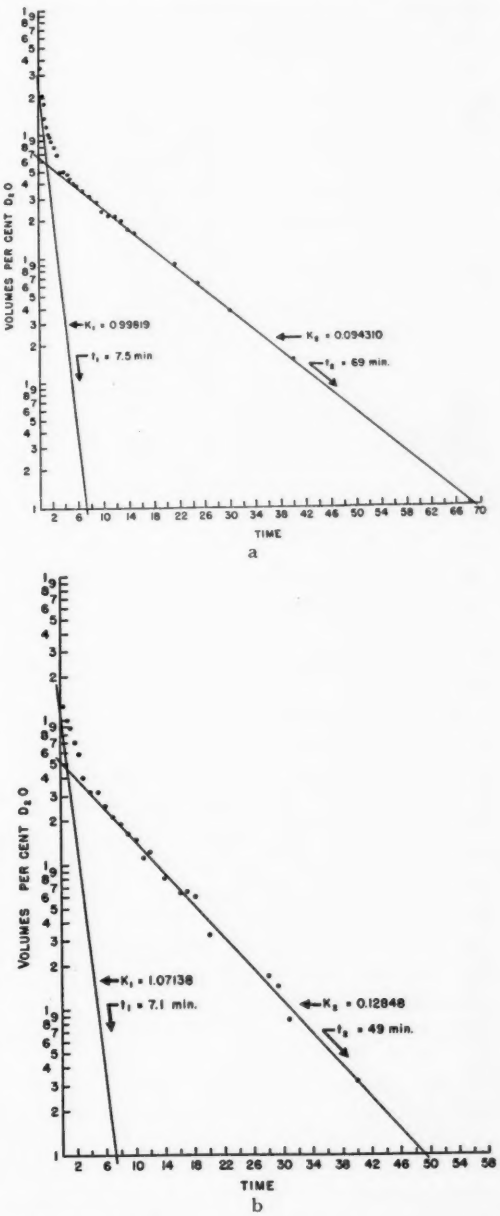

FIG. 2. The fitted components of the equilibration curves in dog 1-D: a, before, and, b, after dialysis.

experimental animal was given 20 milligrams of heparin through the venous cannula at the onset of dialysis, and 5 milli-

TABLE I.—TOTAL EXCHANGEABLE POTASSIUM AND AMOUNTS OF POTASSIUM REMOVED BY DIALYSIS IN EACH EXPERIMENTAL ANIMAL

Dog No.	*Potassium removed by dialysis, mEq.*	*Total exchangeable potassium (K_e)*	*K_e removed, per cent*
1	45	42.24*mEq./kgm. or 359 mEq./kgm.	12.53
2	65.2	42.24*mEq./kgm. or 908 mEq.	7.18
3	None Control	40 mEq./kgm. or 727 mEq.	. . .
4	Control		
5	51.4	42.24*mEq./kgm. or 877 mEq.	5.86
6	Samples inadequate 45.0	54 mEq./kgm. or 847 mEq.	5.31
7	45.1	42.2 mEq./kgm. or 701 mEq.	6.43
8	Control		
9	57.4	35 mEq./kgm. or 651 mEq.	8.82
10	41.5	42.2*mEq./kgm. or 832 mEq.	4.99
11	44.8	42.2*mEq./kgm. or 752 mEq.	5.96
12	Control		
13	Control		

*Starred figures are the mean of our exchangeable potassium determinations on a wt. basis.
Mean per cent removed—7.14.

grams hourly thereafter throughout the procedure.

Tap water, previously treated with a potassium removing cation exchange resin, was used to fill the 100 liter bath of the artificial kidney. In the potassium depletion dialyses, Na^+, Ca^{++}, Mg^{++}, HCO_3^-, Cl^-, HPO_4^{--}, SO_4^{--}, dextrose, urea, and creatinine were added to the bath in such quantities that the resultant bath concentrations were identical with the concentration of these substances in the blood.[1] The baths used in the control group were similarly constituted except that K^+ was added in physiologic quantities.

The baths were changed at 2 hour intervals according to the procedure advocated by Wolf and associates. Samples of blood and dialysate for the determination of the various electrolytes were obtained at the beginning and end of each 2 hour bath and usually at more frequent intervals. Blood samples were obtained from the arterial cannula and the dialysate samples were taken from a representative portion of the bath. Using these values, the total quantity of K^+ removed could be determined. In addition, a check could be made on the constancy of the other electrolytes. Occasionally, hemolysis was noted toward the end of the dialysis. However, the animals seemed to experience no untoward effects, and since the concentration of K^+ within the red blood cells of the dog is the same as in the plasma, hemolysis presumably did not affect the potassium analyses. Blood flow through the machine averaged 200 cubic centimeters per minute, as determined by a flow meter, and the average total dialysis time was 6 hours. Approximate blood pressures were recorded by an aneroid manometer attached to one end of a heparin filled polyethylene tubing, the other end of which was attached to a T tube inserted into the arterial cannula. Readings were made when the flow of blood distal to the T tube was obstructed by a clamp.

The only serious untoward effect observed during dialysis was a tendency for most of the animals to become hypotensive during the first 10 minutes of procedure. Occasionally, the hypotension would respond when the dialysis was stopped, but on other occasions it was necessary to administer vasoconstrictor drugs such as noradrenalin. The smaller the experimental animal, the more susceptible it seemed.

Following the termination of the run, the cannulas were removed and the vessels tied off. The ligation of the femoral vessels never produced evidence of ischemia in the leg. This ligation could conceivably have had an effect on the speed of water equilibration, but since an identical procedure had been employed in all of the experimental animals, this effect can be considered controlled. All incisions were closed with interrupted vertical mattress sutures of silk and the dog placed in a cage with a pan of distilled water available.

On the morning after dialysis the identical procedures which had been done during the predialysis runs were again per-

[1]In the case of $Na+$, the depletion bath concentration was the sum of the blood's $Na+$ and $K+$ concentrations.

formed; these included the volumes of distribution of Evans blue, sucrose, and D_2O. The animals tolerated this procedure well. Figure 1 is a characteristic example of the predialysis and postdialysis curves obtained in the depletion experiments. The mathematical analysis of the equilibration characteristics of the D_2O curves was done by the technique outlined previously.

These analyses and indices having been obtained, it was then possible to compare the predialysis and postdialysis results, pairing the values obtained for each dog.

RESULTS

Table I shows the results of dialysis in the individual animals. It will be noted that the total exchangeable potassium (K_e) was actually determined in only 4 animals. The mean exchangeable potassium for these 4 expressed in milliequivalents per kilogram has been used to calculate the approximate K_e for the remainder of the animals. This mean value agrees closely with human estimates. The average fraction of the K_e removed by dialysis was 7.14 per cent (range: 5 to 12 per cent).

Table II shows the values obtained before and after dialysis for the volumes of distribution of Evans blue, sucrose, and deuterium oxide, as well as the whole blood volumes (calculated from the hematocrits) and the weights. In the only instance (dog 9-D) in which there was an apparent gain in weight coupled with a loss of total body water the animal had gained considerable weight between its first and second dialyses. A "C" beside the dog number indicates that that particular experiment was a control dialysis, and a "D" that the animal was depleted of potassium.

The changes in these various indices as a result of dialysis are indicated in Table III. Here the figure for each index is expressed as per cent gain or loss from the predialysis figure.

Table IV shows the statistical comparisons which were made of the differential behavior of the fluid compartments incidental to control and depletion dialysis, using the percentage figures given in Table III. The statistical comparisons were done by means of "t" tests between averages of the percentage difference for the depletes on one hand and the controls on the other.

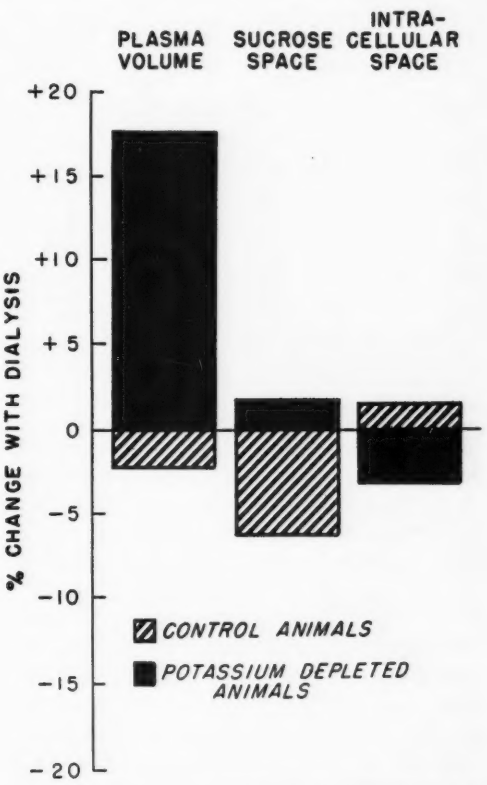

FIG. 3. The mean percentage change in the fluid compartments relative to the total body water (the mean percentage change in any fluid compartment minus percentage change in total body water).

Figure 3 is a graphic summary of the evaluation which was made of the dependence of three compartments upon increments or decrements in the total body water. The method used was to obtain an estimate of change for each compartment in every animal by comparing the value for that compartment (in per cent change) with the per cent gain or loss of total body water incidental to dialysis. Thus, if the plasma volume increased 10 per cent in the presence

TABLE II.—PREDIALYSIS AND POSTDIALYSIS VALUES

	Predialysis					*Postdialysis*				
Dog No.	*PV*	*BV*	*Sucrose space*	*Total body water*	*Weight*	*PV*	*BV*	*Sucrose space*	*Total body water*	*Weight*
1-D.....	426	711	2.62L	5.01L	8.5	492	820	2.85L	4.77L	8.0
2-D.....	1.140	2.170	4.99L	13.37L	21.5	1.220	2.280	4.69L	10.15L	19.9
3-C.....	1.565	2.650	4.52L	13.44L	18.2	1.109	1.695	3.47L	13.49L	18.0
4-C.....	1.035	1.700	3.77L	12.45	16.8	1.190	1.630	3.40L	10.52	17.2
5-D.....	1.350	2.350	4.50L	15.10	20.8	1.360	2.370	4.64L	12.90	19.6
6-D.....	.886	1.477	3.08L	10.50	14.1	.929	1.408	3.25L	11.0	13.8
7-D.....	.907	1.680	3.16L	10.80	16.6	1.290	1.980	3.24L	9.52	14.3
8-C.....	1.315	2.087	4.21L	12.83	15.7	.815	1.700	3.61L	13.33	15.6
9-D.....	1.210	2.090	4.99L	14.58	18.6	1.340	2.436	3.88L	13.13	19.3
10-D.....	.377	1.624	4.81L	12.09	19.7	1.035	1.917	3.03L	11.77	17.3
11-D.....	1.223	2.109	3.79L	15.74	17.8	1.050	1.960	3.09L	13.20	15.6
12-C.....	1.028	1.869	3.37L	13.10	16.4	1.293	2.351	4.03L	13.45	17.4
13-C.....	1.007	1.550	3.38L	14.53	18.6	1.223	2.283	3.25	14.67	18.5

C=Control.
D=Depleted.

of a 10 per cent decrease in total body water, the result is considered to be a discrepancy in movement of this compartment of approximately +20 per cent in this instance. If the total body water had increased 10 per cent and the plasma volume were up 5 per cent, the result is an approximate −5 per cent movement of plasma relative to total body water. This derived figure was obtained for all dogs and for all three compartments, and results shown in Figure 3.

Table V summarizes the comparison of the characteristics of the equilibration curves of deuterium oxide prior to and following control and depletion dialysis. The evaluation was done as follows: the change in each equilibration characteristic as a result of dialysis (of either type) was expressed as a per cent of the predialysis level. The various percentages (either + or −) so obtained were now subjected to a statistical evaluation in which the control dialysis changes were compared with those induced by depletion of potassium by dialysis. Four comparisons were possible (one for each curve characteristic). The evaluation method consisted of comparing group averages by means of "t" tests.[2] The values were "normalized" by the conversion to percentages since we place equal weight on the four characteristics in terms of physiologic significance, and a reduction to equivalent dimensions makes this point of view less difficult to express. Furthermore, the values for the slopes are handled with greater facility in these dimensions.[3] It is evident from this table that highly significant differences exist between the curve characteristics secondary to control and depletion dialysis respectively. A set of such curves is shown graphically in Figure 1. This figure illustrates the characteristically increased speed of equilibration which is a reproducible effect of potassium depletion. Each animal had a distinctive pattern of equilibration; therefore, subtle differences induced by the experimental conditions are obscured by the animal-to-animal changes unless the comparisons are based on the paired data obtained in the same animal before and after dialysis.

[2] The standard errors of the rate constants (K_1 and K_2) were of the same low order of magnitude from run to run. The use of these standard errors in comparing the constants of the curve would have resulted in greater statistical significance than obtained by the present analysis which includes dog to dog variation.

[3] In the course of this study, the constancy of the number o *turnovers* occurring prior to complete equilibration of substances equilibrating through their volumes of distribution was first noted. This unusual property of such systems will be discussed in considerable detail elsewhere (6). In these curves, the total number of turnovers would be approximately represented by:

$$K_x t_x + K_1 t_1 + K_2 t_2 = T$$

where T=total number of turnovers, and where K_x is the average slope of the concentration curve during injection and where t_x is the time of injection. This factor is not known in these experiments since the D_2O injections were given as rapidly as possible, so the complete evaluation of T was not possible. This first term is relatively constant, however, since the injections were given with essentially identical technique. There would have been variation in K_x had we been able to calculate it due to variation in size of dog and speed of equilibration during this initial interval. Despite these variables, the average value of $K_1 t_1 + K_2 t_2$ for all dogs was found to have a coefficient of variation of 9.5 per cent. As indicated above, this observation led to a more careful evaluation of the constancy of T, and it is now believed that the total number of turnovers of all solutes equilibrating into their volume of distribution is a characteristic constant.

TABLE III.—COMPARTMENTAL FLUID SHIFTS SECONDARY TO DIALYSIS IN PER CENT CHANGE FROM PREDIALYSIS VALUE

Dog No.	*PV, per cent*	*BV, per cent*	*Sucrose space, per cent*	*Interstitial fluid, per cent*	*Intracellular fluid, per cent*	*Total body water, per cent*
1-D	+ 5.39	+15.30	+ 8.78	+ 7.75	−19.65	− 4.79
2-D	+ 6.56	+ 4.82	− 6.02	− 9.86	−34.76	−24.50
3-C	−29.10	−36.20	−23.20	−20.27	+12.32	+ .37
4-C	+13.02	− 3.53	− 9.81	−19.05	−16.80	−15.50
5-D	+ 0.74	+ 0.85	+ 3.11	+ 4.13	−22.05	−14.60
6-D	+ 4.63	− 4.67	+ 5.23	+ 5.98	+ 4.45	+ 4.76
7-D	+29.40	+15.50	+ 2.47	−13.32	−17.80	−11.75
8-C	−37.90	−18.70	−14.25	− 3.46	+11.32	− 0.64
9-D	+ 9.70	+14.35	−22.25	−33.79	− 3.55	− 9.95
10-D	+15.28	+15.30	−37.01	−49.30	+16.70	− 2.66
11-D	−13.94	− 7.09	−18.46	−20.62	−15.40	−16.15
12-C	+20.50	+20.50	+16.39	+17.09	− 3.19	+ 2.67
13-C	+18.31	+32.05	− 3.85	−14.77	+ 2.42	+ 9.62

DISCUSSION

The results of the depletion dialyses compared to the total exchangeable potassiums shown in Table I would seem to indicate that the intracellular potassium, even though exchangeable, is not readily "extractable." Even though the dialyses were carried out against potassium-free baths, an average of only 7.14 per cent of the exchangeable potassium was removed. This observation emphasizes that the large gradient between intracellular and extracellular potassium which exists normally is probably the result of an "active" retention of potassium by the cell. Despite this fact, the large decrements in K_e, which Moore has demonstrated in clinical states of malnutrition, or specific depletions induced by diarrheas or gastrointestinal fistulas apparently show that this cellular resistance to potassium transfer is overcome with time in these circumstances. These experiments indicate that it can be done *acutely* to a limited extent, and they offer information about the effect of this presumptive exchange of Na^+ for K^+ within the cell upon fluid compartmentalization and the water equilibration rates.

The changes in the fluid compartments following the dialyses, shown in Tables II and III and compared in Table IV, show a borderline statistical significance between the changes in intracellular water and total body water induced by control and depletion dialysis respectively. It will be noted that in each of these cases the controls had the larger mean. It is thought that the presence of the essentially normal potassium concentration in the cells of the control animals is responsible for this difference. This hypothesis will be discussed again in detail.

The sucrose space was not significantly different (Table IV) under the various experimental circumstances although the mean decrement was somewhat greater in the depletes. Also, the plasma volume changes were not significantly different despite their striking reversal of the directional changes exhibited by the sucrose space of which this smaller volume is a part.

Figure 3 illustrates the striking *relative* increment in the plasma volume of the depletes which occurred at the same time that the *interstitial* fluid was markedly decreased, and the intracellular fluid was moderately diminished. There was, as noted previously, a definite hypotensive tendency in the depleted animals. This marked dissociation of the behavior of the sucrose space and the plasma volume within it is highly significant; and emphasizes again the finely balanced control of plasma volume presumably dependent on alterations in capillary blood pressure and the relative osmolarity of the plasma and interstitial fluid.

One way of evaluation of these data is to assume a physiologic circumstance consistent with the experimental conditions, and then test the manner in which the data fit this hypothesis. We will examine the mechanisms believed to be responsible for the postulated

TABLE IV.—COMPARISON OF THE COMPARTMENT CHANGES INCIDENTAL TO CONTROL AND DEPLETION DIALYSIS

	Means		
Compartment	*Depletes, per cent*	*Controls, per cent*	*"P"*
1. Plasma volume	+7.22	−3.03	<.5>.4*
2. Sucrose space	−8.02	−6.94	>.9
3. Intracellular water	−3.12	+1.91	<.10>.05*
4. Total body water	−9.96	− .70	<.10>.05*

*An asterisk signifies that the probability is closer to the figure bearing it.

state of affairs; but let us, for the moment, test the fit of these data to a system which will permit the following, under the experimental circumstances: (1) Under the conditions of dialysis when no potassium has been depleted, the plasma volume will be reduced, while the interstitial fluid and intracellular fluid will increase. Also, the total body water will be slightly reduced. (2) Precisely the opposite changes will occur in those animals from whom potassium has been dialyzed.

The experimental data were tested for their conformation to these assumptions by calculating the change accompanying dialysis for each of these compartments in the individual animals. The depletes and the controls were then segregated, plus signs were assigned to the changes in the depletes if they moved in the expected direction and negative signs if they did not, while a negative sign was used for the controls which moved as predicted, and vice versa. These values were then expressed as per cent of the predialysis level in order to normalize the dog-to-dog and compartment-to-compartment variability in absolute size; and the entire series from the depleted animals were compared with those from the controls by means of a "t" test. The probability that the differences could have arisen by chance is found to be about 1 in 50, or $\leq .02$.

This evaluation of the data would therefore suggest that the differences which have been observed in the various fluid compartments between the control and depletion dialyses respectively could not have occurred through chance. Subsequently, we shall postulate physiologic mechanisms which are consistent with these experimental observations since the assumptions listed under (1) and (2) in the foregoing appear fruitful.

Table V indicates the changes in the characteristics of the deuterium oxide equilibration curves which occurred under the experimental conditions. The means are expressed as the average of the percentage changes from the predialysis run to the postdialysis determination in each experimental animal; and the "p" value represents the probability that the observed differences were the result of chance (calculated by the "t" test). It is evident that all of these differences are significant. This means that the equilibration of water was speeded by the substitution of Na^+ for K^+ in the cell. This was evidenced by steeper slopes for the two components (K_1 and K_2) as well as shorter "extinction times" (t_1 and t_2 as defined before). Whatever the mechanism, it appears definite that the experimental conditions have altered the characteristics of the cellular barrier. Further consideration of this matter follows.[4]

INTERPRETATIONS

The evaluation of these experimental findings appears to depend on the assumption of the lack of free potassium exchange across the cell wall, together with the osmotic consequences.

The patterns of fluid compartmentalization which occur with and without relative potassium depletion are evidence of this dependency. When the intracellular potassium is at a relatively normal level, the dehydrating influence of dialysis (produced by somewhat higher pressures within the dialysis tubing than in the bath, in the presence of essential osmotic equilibrium) is maximally felt in the extracellular compartment. This is presumed to be due to the failure of potassium to leave the cells at the same rate as the water and Na^+ are leaving the extracellular

[4]The transcapillary and transcellular rates of water transfer may be calculated employing appropriate modifications of Flexner and his associates' equations on the transfer of radioactive sodium. These rates can be demonstrated to be greater in the presence of K+ depletion (12).

compartment. This means that the osmotic relationships will oppose the movement of water out of the cell, and the results indicate such a tendency (Fig. 3). In fact, there was a mean gain of +1.91 per cent in the calculated intracellular water volume despite a mean decrease of 0.70 per cent in total body water and of 6.9 per cent in the extracellular space (Table IV).

When a relatively small amount of potassium has been removed from the cell by dialysis, the mean change in the stability of the intracellular water volume is very close to the usual level for statistical significance (Table IV). Also, the increased ease with which water is extracted from the intracellular compartment (and, therefore, from the total body water) is reflected in a greater loss of total body water.

This latter circumstance is presumed to be due to the failure (in the controls) of intracellular water to dilute the extracellular phase as the initial hydrostatic loss of water occurs. The extracellular osmolarity therefore rises, preventing further water losses. In the depletes, no such brake on water loss apparently exists. Presumably, this is due to the removal of intracellular potassium.

The changes in the plasma volume serve as a striking reminder of the role played by the blood pressure (or more accurately the capillary pressure) in the preservation of the plasma volume at its usual level at the expense of the interstitial or intracellular fluid. The animals in the depleted group, as would be expected from their greater loss of total body water (and the physiologic derangement of K depletion) exhibited a greater incidence of hypotension than did the controls. The effectiveness of the osmotic gradient between plasma and interstitial fluid in the maintenance of the volume of the former is, therefore, demonstrated in these experiments.

These findings contrast with the conclusions of Clark and associates that a plasma volume (and blood volume) depletion is the central problem in malnourished and chronically ill patients. It must be remembered that the calculations by which their conclusion was reached were based on the assumption that it is proper to measure the plasma volume and then calculate the estimated volume deficit on the basis of the presumptive size of this compartment prior to the loss of weight. This assumption would appear erroneous, in view of the more vascular nature of the tissue lost in malnutrition than much of that remaining (such as bone). It is true that there are certain tendencies in weight loss patterns which would act in the opposite direction, such as the greater vascularity of viscera over muscle and fat. It is interesting that Clark and his co-workers obtained figures which were normal or high when they calculated the plasma volume on the basis of the actual weights of their patients. Because of the complex compositional alterations which occur with major weight changes, the selection of one method of calculation is certainly difficult; but it seems inaccurate to assume that the plasma volume should be the same despite large losses of differentially blood vessel bearing tissue! Certainly, it would be a most unusual thing for the plasma content of the tissue lost to be equivalent to that retained. These remarks do not at all contradict the notion that it is wise to transfuse a malnourished, ill patient prior to operation. It is desired merely to emphasize that the experimental evidence indicates that the principal changes in fluid compartmentalization take place in the interstitial fluid rather than in the plasma volume. Indeed, in these experiments, the plasma volume responded to losses of interstitial fluid, with increases (depletes), or a damp-

TABLE V.—COMPARISON OF THE CHANGE IN THE CHARACTERISTICS OF THE EQUILIBRATION CURVE FOLLOWING DIALYSIS WITH AND WITHOUT POTASSIUM DEPLETION

Comparison	*Means as per cent change from predialysis run*	*Significance expressed as "P"*
1. K_1 (controls)	−35.36	<.001
K_1 (depletes)	+62.78	
2. K_2 (controls)	−25.09	
K_2 (controls)	+66.00	<.025;> .02
3. t_1 (controls)	+88.96	
t_2 (depletes)	−23.49	<.05; >025
t_2 (controls)	+16.21	
t_2 (depletes)	−27.50	>.001

ened loss (controls) relative to the interstitial fluid. This concept is also supported by the data on volumes of distribution of Evans blue, sucrose, thiosulfate, and deuterium oxide obtained at this Unit on severely burned patients at varying intervals after burning (11). There is also little doubt that comparisons of plasma volume to interstitial fluid volume ratios are an inaccurate method of demonstrating reductions in plasma volume since such a method assumes: (1) that the measurement of the interstitial fluid is correct, and (2) that this compartment is stable. Both of these assumptions are in error, the volume of the interstitial fluid being the most labile of the three principal compartments, and the measurement of this space subject to technical difficulties far greater than the estimation of plasma volume. For example, when sodium thiocyanate is used (as in the data of Clark and associates), it is known (11) that in states of chronic malnutrition the thiocyanate distributes itself into a portion of the cell water, thereby making a ratio between its volume of distribution and that of Evans blue meaningless in deciding on the relative magnitude of the plasma volume. The increased volume of distribution of thiocyanate (and thiosulfate) under these conditions is probably due to replacement of intracellular K^+ by Na^+ in much the same manner as has been accomplished experimentally here (but over a much longer period of time).

When one transfuses a chronically ill patient, one is injecting the red cells into the intravascular compartment, but the water, minerals, and contained organic compounds (including protein) are distributed differentially into the total body water. It is therefore inaccurate to speak of replacement of plasma volume as if the vascular compartment were an impervious tube, or as though the biochemicals and minerals so injected were without physiologic effect. The value of preoperative transfusion appears linked to the replacement of red cell mass, and to its overall biochemical effects more than to a replacement of plasma volume. Indeed, thermodynamic considerations of Starling's hypothesis make it clear that changes in plasma volume which one would predict on the basis of infused plasma will not be met because of changes in the other variables affecting the capillary equilibrium between plasma and interstitial fluid, most notably rises in the capillary pressure. These changes will produce a redistribution of the fluids and noncolloids administered to the interstitial fluid, whereupon similar compensatory changes will alter the intracellular fluid. In short, while the recommendation of transfusion for malnourished, cachectic patients is empirically a good one, the rationale given by Clark and associates (i.e., to build up a lowered plasma volume) seems incorrect. It is certain, however, that adequate replenishment of depleted interstitial and intracellular water, minerals, and protein will result in a more adequate physiologic reserve against operative stress of whatever character. These data would appear to indicate that a diminishment of intracellular potassium plays an important role in the syndrome of "chronic shock."

It can be seen from Figure 3 and Table IV that in the depletes, the plasma volume and sucrose space increase, and that the intracellular water decreases relative to the movement of total body water, while opposite effects were noted in the controls. This phenomenon can also be explained by the lack of potassium exchange across the cell wall. Since a portion of the intracellular potassium has been removed and presumably replaced with sodium, one would expect that the dehydrating effect of dialysis will be maximally felt in the intracellular water with a compensatory increase in the plasma volume due to the observed decreases in the blood pressures and to the resultant osmotic shift of fluid to the intravascular compartment. In the controls, in which there is an essentially normal intracellular potassium, the lack of free diffusibility of this intracellular cation results in a less free egress of intracellular water and the principal loss is therefore suffered by the extracellular phase.

It is interesting to notice that it is necessary to postulate that the intracellular potassium is both not readily diffusible (albeit exchangeable) and also osmotically active. Since it is difficult to conceive of this as an entirely passive circumstance, we must presume that the cell is producing this state in an as yet unclear manner involving energy expenditure.

The observed alterations in the speed of water equilibration in the two series also tend to support the concept of free Na^+ access *to* (within the permitted osmotic limits) and limited K^+ egress *from* the cell. In the depleted animals, in which there has been a reduction in intracellular potassium (and a presumed replacement with sodium ion), the speed of water equilibration was increased. This presumably is due to the fact that Na^+ and its water of hydration are exchanging across the cell wall at a faster pace than they do in the presence of the lower intracellular concentration of Na^+ which existed in the control group. It may also be due in part to an increased hydration of the Na^+ ion as compared to the K^+ ion, such as can be noted by comparing these characteristics of the two ions as demonstrated in transference measurements. The relative hydrations of the two molecules are reported as follows:

$$Na^+: \quad 2.0+1.61X$$
$$K^+: \quad 1.3+1.02X$$

where X = the mean number of molecules of water per chloride ion.

It can therefore be seen that, even if there were no differential ease of passage across the cell membrane, the loss of K^+ into the dialyzing fluid and a substitution of Na^+ ion would result in a slightly increased speed of water equilibration due to the greater water exchange rate per unit exchange of cation. This statement assumes essentially equality of diffusion rates. Actually K^+ diffuses more rapidly[5] than Na^+, so that the effect of the state of hydration of these ions seems insufficient to explain these changes. One must conclude that the freedom of access to the cell by the sodium ion and the relative imprisonment of its analogous cation, potassium, are also responsible for the interesting effects of potassium depletion upon water equilibration rates.

What can be said to have been proved by these studies which will help in the evaluation of the clinical status of potassium depletion? If the human in circumstances suggesting the possibility of K^+ depletion responds to a transfusion or infusion in the manner described at the start of this article, it seems permissible to draw certain tentative conclusions. For example, there is reason to feel that situations tending to cause aggregate water loss will be felt more severely in the presence of K depletion (viz., the loss of total body water in these two series illustrated in Table IV). Therefore, it is probable that by the time such a K^+ depleted individual has begun to exhibit a low blood pressure, his intracellular water and his interstitial water may have been markedly reduced. It is interesting to notice (in Table IV) that the sucrose space is depressed most of all in the deplete group, despite the increase in the intravascular compartment. This observation must mean that, in these circumstances, water is principally lost from the interstitial fluid, the osmotic gradient between plasma and interstitial fluid becoming more effective in the presence of a declining blood pressure.[6] Therefore, infused water will raise the blood pressure to a normal level while it is entering the vascular compartment, but this will not be a lasting effect since the rising blood pressure accelerates the egress of water from the plasma volume. The infused water, therefore, is distributed into the interstitial fluid on the basis of increased hydrostatic pressure, and into the intracellular fluid because the resultant dilution of the interstitial fluid makes the intracellular water hypertonic to its surroundings. In this manner, the infused water is distributed into the total body water,

[5] Potassium hydrate: 1.72 square centimeters per day at 12 degrees C. and 1.0 gram molecule per liter; and sodium hydrate: 1.11 square centimeters per day at 12 degrees C. and 1.0 gram molecule per liter. The ratio is less marked with other compounds such as the chlorides.

[6] This neglects the possibility that ionic concentration change will affect membrane permeability per se.

but fails to affect the blood pressure appreciably. In a clinical situation this response should be interpreted as an indication that the patient needs relatively more potassium as well as more water. The improvement in vascular tone which follows adequate potassium therapy will also be important in the re-establishment of the normal proportional fluid compartmentalization.

SUMMARY

1. Acute depletions of exchangeable potassium have been accomplished in dogs by means of dialysis against a potassium-free bath on the Kolff-Brigham artificial kidney.

2. A mean of 7.2 per cent of the total exchangeable potassium was removed at each dialysis.

3. The control series showed a definite tendency toward depletion of the extracellular compartment (both vascular and interstitial) with good preservation of the intracellular water volume.

4. The depleted animals lost considerably more of their total body water, the interstitial fluid and intracellular water being the sources of this loss, while the plasma volume tended to increase.

5. The fluid compartments did not behave as a function of the total body water in the same fashion in the two experimental groups; indeed, results were in opposite directions.

6. Exchange of intracellular potassium for sodium results in speeding of the rates of water equilibration which is much greater than can be accounted for through diminution in total body water.

7. Physicochemical mechanisms by which the observed phenomena occur are postulated and discussed.

8. The implications of these data in the etiology of the "chronic shock" syndrome are discussed.

CONCLUSION

The exchange of sodium for intracellular potassium results in marked alteration in the adjustment of the functional fluid compartments to loss of total body water, and produces definite acceleration in the rates of water equilibration. These effects are of greater significance in the production of so-called "chronic shock" than is plasma volume reduction.

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PRIMARY CARCINOMA OF THE OVARY

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THE PRESENT SERIES comprises cases of primary carcinoma of the ovary seen at the Royal Victoria Hospital during the years 1930 to 1954. In every case included in the series, we have reviewed all available data including the pathologic material. Originally, we had approximately 350 cases of ovarian carcinoma, but on critical analysis, about 80 cases were excluded for the following reasons: clinical diagnosis only, initial therapy elsewhere, metastatic carcinoma, dysgerminomas, arrhenoblastomas, granulosa cell tumors, and sarcomas. It was our opinion that the special tumors could not, with absolute certainty, be labelled carcinoma and for this reason were excluded. They will form the material for a future paper.

No case was considered suitable unless either surgery was performed or a postmortem examination done.

With the selection based on the criteria mentioned, we were left with 270 cases forming the material to be discussed.

AGE

The age distribution is seen in Figure 1. It is noted that there is a near perfect distribution curve. The average age was 49.9 years with 62.6 per cent of patients in the age range from 40 to 59 years. The youngest patient was 15 and the oldest was 82 years old. Our findings are similar to those in many other series.

MARITAL STATUS AND GRAVIDITY

Married patients comprised 78.9 per cent of the cases, similar to findings in other series. In this group of 213, there were 7 previously gravid but nulliparous patients and 35 nulligravid patients. In 9 there was no information regarding parity. Thus, the infertility rate of 20.6 per cent was considerably less than that reported by Lynch, Meigs, Allan and Hertig, Munnell (11), and Dockerty. Our results are almost identical with values given for the general population (20.3 per cent), a finding similar to that reported by Wheelock and associates. Graphs showing distribution of the number of pregnancies and the number of abortions indicate a conformity with similar graphs for the general population. The peak in gravidity was 17; the greatest number of abortions was 9. We do not believe there is any inherent defect in germ plasm explaining both infertility and origin of carcinoma as some have stated.

SYMPTOMATOLOGY

Figure 2 shows the distribution of duration of symptoms, the latter being based on the date of admission to the hospital. It can be seen that the peak grouping is 1 to 3 months with 36.3 per cent of all cases presenting by the end of the second month. This finding is similar to that of Allan and Hertig, Helsel, and Schmitz. The average duration of symptoms in our series was 9.7 months.

Symptomatology is depicted in Figure 3 and Table I. Abdominal pain, which consisted usually of crampy lower abdominal pain but which also included upper abdominal pain, sensation of pelvic pressure, and "tightness," was the most prominent symptom. Abdominal swelling included a palpable mass and ranked second in prominence. All other symptoms were present in considerably less incidence. We were not

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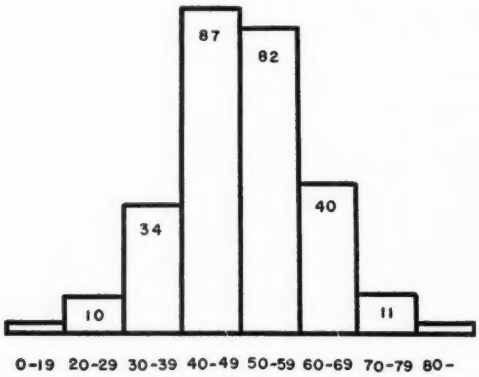

FIG. 1. Age incidence. Number of cases by decades.

impressed with the prominence of vaginal bleeding, either premenopausal or postmenopausal. It was interesting that leg pain or swelling was present in 14 cases, all of these showing spread beyond the confines of the ovary. The prominence of abdominal pain and swelling is similar to that found in many other series, although one or the other may be found in a greater number of cases. It can be repeated again that there are no characteristic symptoms, although the presence of abdominal pain *and* swelling is strongly suggestive. In the cases of shorter duration we were impressed with the high incidence of abdominal pain, usually crampy, often localized to the side of the tumor (if unilateral) and bearing some resemblance to an acute abdominal episode.

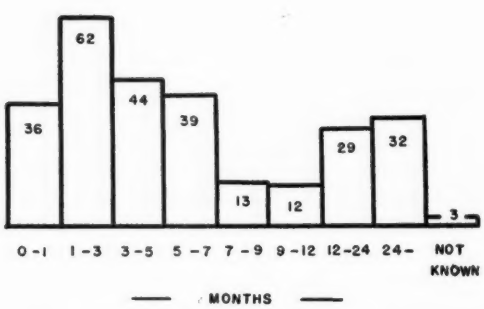

FIG. 2. Duration of symptoms. Number of cases in various month groups.

FAMILY HISTORY

In 47 cases, the family history for cancer was positive; in 184 cases it was negative; and in 39 cases no family history was given.

Our percentage of positive family histories falls far below the values which were given by Lynch and Pearse and Behrman, and, we believe, is not a significantly high incidence.

CLINICAL STAGING

It may be advantageous by way of introduction to explain how our method of staging the extent of advancement of the disease was evolved. Before any cases were analyzed, and even before the literature was reviewed, we decided to stage ovarian carcinoma, basing this staging strictly on theoretic grounds. Like carcinoma of the cervix, our stages follow the degree of spread of the disease; unlike cervical carcinoma they are based solely on operative findings. As will be shown later, our survival rates computed for the individual stages correlated extremely well with the theoretic stages.

Stage 0.....Carcinoma in situ with no invasion of the stroma.
Stage I.....Grossly malignant but confined to the ovary. It can be either solid or cystic with no excrescences or infiltrated adhesions.
Stage II.....Breakthrough of the ovarian capsule: excrescences, infiltrated adhesions, ruptured capsule (before or at operation). No manifest spread beyond the ovary.
Stage IIA.....Bilateral ovarian involvement without evidence of any other pelvic metastases.
Stage III.....Pelvic dissemination: tubes, uterus, other ovary, bladder, rectum, rectosigmoid, pelvic peritoneum.
Stage IV.....Metastases beyond the pelvis.
Stage IVL....Liver involvement.

TABLE I.—INCIDENCE OF THE MAIN SYMPTOMS

Symptoms	*Per cent*
Abdominal pain	61.4
Abdominal swelling (including palpable mass)	56.3
Anorexia, malaise, weakness	24.1
Gastrointestinal	24.1
Urinary	21.1
Loss of weight	19.6
Menstrual disturbances	13.3
Postmenopausal bleeding	13.0
Back pain	10.0
Leg pain and/or swelling	5.2
Fever	1.5

Stage 0 is similar to stage 0 in the cervix with the question of undisputed malignancy unsettled but suggestive. State IIA appears to be a special group, a definite intermediate group; we will not speculate on its pathogenesis. We believed that the presence of liver involvement justified the setting up of a special stage to denote its presence.

A review of the literature presented some interesting facts. First, there is no uniformity of opinion regarding staging of the disease. Second, the defect in every classification presented is that they fall back on criteria of operability which are far from standardized. It is our opinion that, like staging for carcinoma of the cervix, the classification should be based on the clinical findings only. The Munnell and Taylor classification (12) is similar to ours, but certain basic differences are present.

In Figure 4 our cases are broken down by stages. It is distressing to see that stages IV and IVL combined comprise almost 40 per cent of the cases, while unilateral involvement is present in almost 35 per cent of the cases.

Little correlation with age is present, except that with advancement of disease the peak age group moves up from the fifth to the sixth decade. The difference is not very significant.

Figure 5 shows a comparison of stage with duration of symptoms. It is readily seen that no true correlation is present; all stages show a similar picture. Therefore, and this is disturbing, the very fact that a patient has a short history does in no way offer assurance that the malignancy has been discovered early.

TABLE II.—TYPE OF SURGERY

	No.	*Per cent*
Unilateral salpingo-oophorectomy		
Only	49	18.1
With subtotal hysterectomy	7	2.6
With total hysterectomy	1	0.4
Total	57	21.1
Bilateral salpingo-oophorectomy		
Only	54	20.0
With subtotal hysterectomy	48	17.8
With total hysterectomy	46	17.0
Total	148	54.8
Laparotomy	59	21.9
Miscellaneous	6	2.2

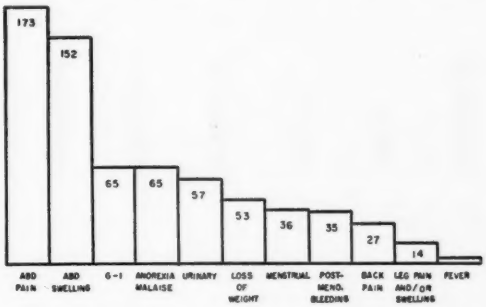

FIG. 3. Symptoms. Number of cases of various main symptoms.

A detailed study of symptomatology in the various stages was undertaken. Little correlation was noted with these exceptions: abdominal pain and swelling are slightly more common, while anorexia and loss of weight are considerably more common with advancement of the extent of the disease. The latter findings are predictable.

TYPE OF SURGERY

In Table II, the various types of surgery performed are detailed. It should be mentioned that among the cases of unilateral adnexal removal are some in which the patient was inoperable and the adnexa was removed palliatively because of the presence of a large cyst which could cause obstructive symptoms. We are unable to state whether

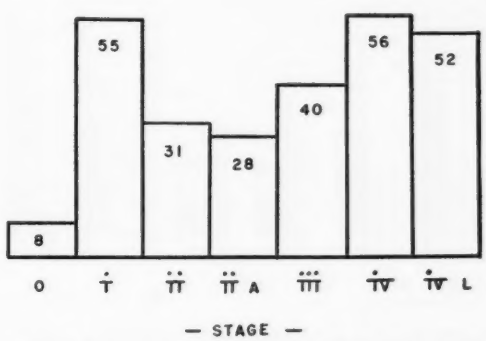

FIG. 4. Clinical stages. Number of cases of each clinical stage.

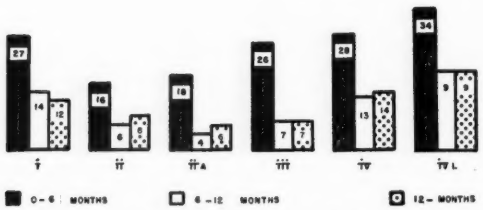

FIG. 5. Clinical stages correlated with duration of symptoms. Number of cases in the 3 main month groupings.

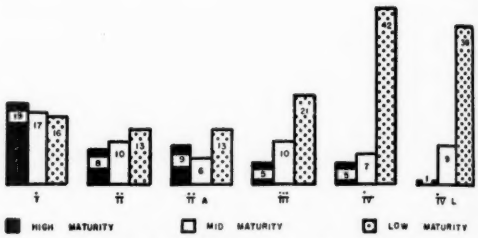

FIG. 7. Clinical stages correlated with histologic grading. Number of cases of high, mid, and low maturity in each stage.

subtotal is inferior to total hysterectomy; our statistics do not permit this type of analysis to be made.

We agree with other authors in advocating total hysterectomy with bilateral salpingo-oophorectomy as the optimum method of surgical approach. The modifications regarding unilateral adnexal removal for cases in stages 0, I, and II are acceptable in young women desiring a family.

X-RAY THERAPY

During the period from 1930 to June 30, 1950, 56 of 202 patients, in addition to surgery, received radiation therapy for an incidence of 27.7 per cent. In the majority, this treatment was immediately postoperative, while in others it was withheld until deemed necessary. A few patients received more than one course of roentgen therapy. Dosages ranged from 6,000 to 16,000 roentgens in air with tumor doses of 1,000 to 3,500 roentgens. Prior to 1939, standardization was not present. Our methods of utilization of x-ray correspond with those mentioned in many other articles.

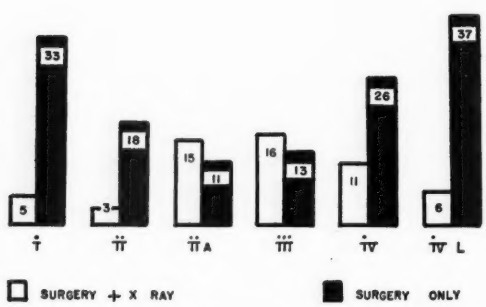

FIG. 6. Clinical stages correlated with treatment (1930 to 1950). Number of patients receiving surgery only or surgery and x-ray in each stage.

CLINICAL STAGES AND TREATMENT

In Figure 6, an analysis of treatment by stages is given. It can be seen that surgery by itself is most prominent in the early and the late stages, while in IIA and III, x-ray supplements are more common. We should mention that in stages IV and IVL, many patients were too ill to receive x-ray therapy or died before such treatment could be contemplated.

PATHOLOGY

In every case the microscopic material was reviewed, except in the 7 cases in which no specimen was obtained. These latter cases were worthy of inclusion, even though no pathologic confirmation was at hand, since the operative findings were characteristic of the disease. An attempt was made to define all anaplastic cases as either serous or pseudomucinous, though the difficulties inherent in such a practice were known to us. We admit that mistakes are probable, even though many opinions were sought in extremely difficult cases, but such an attempt is preferable to having an unclassified group. In the anaplastic group, certain features, such as vacuolation and cytoplasmic and nuclear characteristics, appeared with regularity in one or the other group, and when possible special stains helped to confirm initial impressions. It was gratifying

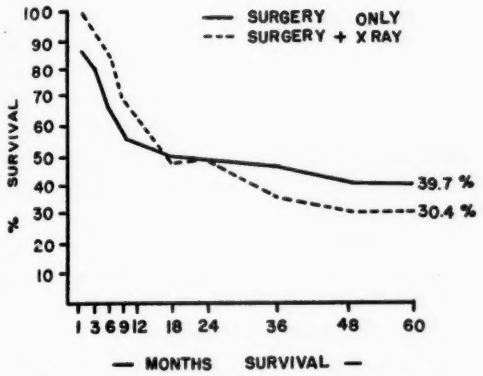

FIG. 8. Per cent survival by months correlated with the treatment which was received (1930 to 1950—all stages).

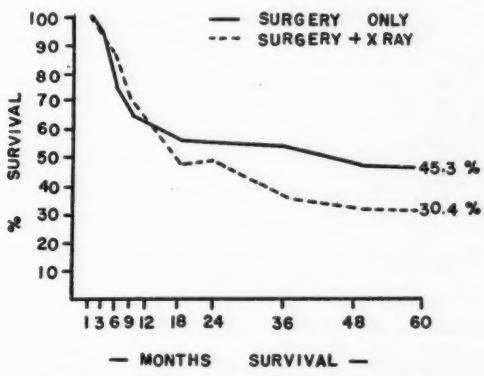

FIG. 9. Per cent survival by months correlated with treatment. All deaths within 30 days of admission excluded (1930 to 1950—all stages).

that the criteria set up for differentiation remained consistent and appeared consistently in the later stages of the study of the slides.

Histologic grading was set up in three groups—high, mid, and low maturity—based on the usual criteria of differentiation and mitotic activity, and these groups parallel those defined by Munnell and Taylor (12) and Montgomery.

In Table III our findings are presented, which are essentially similar to the findings of other authors. Certain differences are present: First, our incidence of pseudomucinous type is higher. Second, the other authors all have a considerable number of unclassified cases. Third, other series contain a significant percentage of cases excluded from our series. Adenocarcinomas comprise 95.3 per cent of our cases. We believe that the 6 special carcinomas listed should be included, since no doubt exists about either their malignancy or the fact that they are primary.

In Figure 7, the clinical stages are compared with histologic grading. It is noted that in cases with dissemination there is a significantly high incidence of cases of low maturity. Whether this observation implies a positive correlation is difficult to ascertain, for a case could either be a stage IV because it is of low maturity, or low maturity because by the time it is stage IV it has become anaplastic. However, there is no disputing the fact that the more anaplastic the tumor the more likely it will be an advanced case. On the other hand, it cannot be overlooked that cases of low maturity may also be seen in stages I and II.

DOUBLE PRIMARIES

Sixteen cases of the 270 satisfied the criteria for double primary neoplasms, an incidence of 5.9 per cent. Included were 5 breast cancers, 3 colonic cancers, 4 rectal carcinomas, 1 carcinoma in situ of the cervix, and 3 endometrial carcinomas.

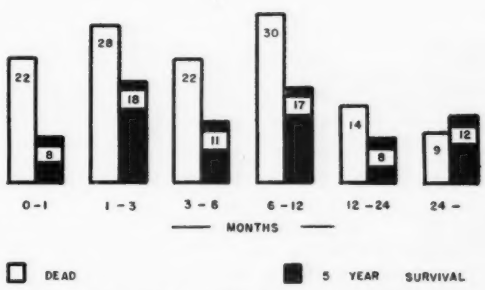

FIG. 10. Prognosis correlated with duration of symptoms (1930 to 1950). Number of patients, dead and living 5 years, in the main month groupings.

TABLE III.—TYPE OF PATHOLOGY

	No.	*Per cent*
Serous adenocarcinoma		
High maturity	27	10.0
Mid maturity	27	10.0
Low maturity	100	37.1
Total	154	57.1
Pseudomucinous adenocarcinoma		
High maturity	28	10.4
Mid maturity	31	11.5
Low maturity	41	15.2
Total	100	37.1
Combined serous and pseudomucinous		
Mid maturity	1	
Low maturity	2	
Total	3	1.1
Miscellaneous		
Squamous cell carcinoma (in dermoid)	2	
Malignant teratoma	3	
Transitional cell carcinoma	1	
Total	6	2.2
No specimen	7	2.5

PREVIOUS PELVIABDOMINAL SURGERY

We were interested to ascertain in how many cases previous abdominal surgery had been performed for diseases (benign) of the internal genitalia. Here, an opportunity was present for complete extirpation of the generative organs but this procedure was not done for a variety of reasons. A summary of these cases appears in Table IV.

The 15 cases out of a total of 270 cases give an incidence of 5.6 per cent. In only 9 cases, however, was a hysterectomy previously performed, an incidence of 3.3 per cent, similar to Counseller's incidence of 4.5 per cent. The prime consideration, however, is that in 8 cases the women were less than 40 years old and, therefore, more radical surgery would not have been contemplated anyway. In addition, 2 other patients were less than 44, an age sometimes used as an arbitrary upper limit for the retention of the ovaries. Therefore, in two-thirds of these cases nothing more could have been done. However, in the other 5 cases, carcinoma of the ovary could have been prevented by a more radical approach at the initial operation; for example, one may question the saving of an ovary in a woman of 57 as was done in 1 case. An interesting case is one in which complete extirpation was performed in a woman of 41 with the exception of a small stump of the left ovary which became carcinomatous within 6 years.

TABLE IV.—PREVIOUS PELVIABDOMINAL CASES

Age at 1st operation, yrs.	*Age at cancer, yrs.*	*Type of operation*
15	29	Uterine suspension
49	72	Hysterectomy (fibroids)
38	60	Right salpingo-oophorectomy
50	62	Subtotal hysterectomy, right salpingo-oophorectomy
49	54	Subtotal hysterectomy, right salpingo-oophorectomy
34	39	Subtotal hysterectomy (fibroids)
36	56	Left salpingo-oophorectomy (cyst)
19	42	Oophorectomy
45	53	Hysterectomy (fibroids)
41	47	Subtotal hysterectomy, bilateral salpingo, right oophorectomy, partial left oophorectomy
25	45	Right oophorectomy
36	44	Subtotal hysterectomy (fibroids)
57	61	Hysterectomy, left salpingo-oophorectomy
44	70	Hysterectomy (fibroids)
25	45	Right oophorectomy

Age at initial operation: under 40 years, 8; 40 to 44, 2; 45 to 49, 3; 50 and over, 2.

Randall, on the basis of a statistical analysis of New York State Census Surveys states "unless it can be shown that after her climacteric the woman derives no benefit from the preservation of her ovaries, we believe their prophylactic removal seems unwarranted by the mere probability of ovarian pathology."

SURVIVAL RATES

There were 202 cases from 1930 to June 1950, and these comprise the group in which study of survival rates is possible because of the necessary 5 year lapse. One case was followed 37 months and then lost. This patient is considered as dead at the time of last contact. In addition, before the advent of our Central Tumour Registry, 2 other cases were not followed at all. These women were considered dead at the date of discharge from hospital. Thus a 5 year follow-up is available in 98.5 per cent of the cases.

Our survival rates are summarized in Table V.

Our overall 5 year survival rate of 37.6 per cent compares favorably with other rates in the literature which are presented in Table VI.

It should also be pointed out that in 2 of the cases considered in Table V as deaths

following surgery the patients were moribund on admission, died shortly afterward, and autopsies were performed. If we excluded these from the comparative statistics, the survival rate with surgery alone would be even higher.

Some may be of the opinion that our stage 0 is not true carcinoma of the ovary. If these cases are excluded, then our overall 5 year survival is 34.5 per cent, still comparing favorably with the literature.

To test the validity of our clinical staging, survival rates were calculated by stages, as is shown in Table VII. Certain comments can be made: Note the excellent correlation between survival rates and clinical stages. Stage 0 like its cervical counterpart offers 100 per cent prognosis. It would appear that stages I and II are not different, except for a slightly better 10 year survival for stage I. The implications are immediately apparent, for evidently the presence of papillary projections on the outside of the tumor or the rupture of the tumor during removal is less cause for concern than previously thought. Stage IIA definitely establishes itself as a distinct entity, intermediate between II and III, but the 10 year survival is similar to stage III, indicating that probably other pelvic metastases are present though not manifest at the initial operation in many of the cases. As is expected, stages IV and IVL shows a poor prognosis. One interesting case is of a patient with a proved stage IV who lived 13 years without any corrective surgery beyond a biopsy, no postoperative irradiation and only periodic paracentesis, and in whom the diagnosis was confirmed at autopsy. One wonders about the two 5 year survivals in stage IVL, for what may have appeared as metastases may not, in fact, have been so.

Figures 8 and 9 show in more detail a correlation between treatment and survival. It would appear in the uncorrected curves that although x-ray therapy does not offer a better 5 year prognosis, it does offer a palliative effect prolonging life. But since 18 patients died within 1 month of admission, they were excluded as they could not even be considered as potential cases for radiation. In the corrected curves it can be seen that radiation therapy fails to show an appreciable effect on prolonging life.

In Figure 10, the prognosis is compared with the duration of symptoms. It would appear that up to 1 year, the short duration

TABLE V.—SURVIVAL RATES IN 202 CASES

	Surgery only (146 cases)		*Surgery+x-ray (56 cases)*		
	No.	*Per cent*	*No.*	*Per cent*	*Total No.*
Dead	88		39		127
Alive 5 years	58	39.7	17	30.4	75 (37.6%)
Alive 10 years	34	32.7*	5	13.9*	39

*Based on 1930 to 1945: surgery only, 104 cases; surgery+x-ray, 36 cases.

TABLE VI.—REVIEW OF SURVIVAL RATES IN LITERATURE

Reference	*No. of cases*	*Alive 5 years Per cent*
Allan and Hertig	265	35.0
Diddle	314	21.3
Freed and Pendergrass	101	37.9
Kerr and Elkins	196	30.4
Lynch	110	35.5
Meigs	154	15.5
Montgomery	107	20.5
Munnell and Taylor (12)	200	27.5
Pearse and Behrman	262	20.6
Schmitz and Majewski	143	20.3
Taylor and Greeley	138	17.4
Walter, Bachman, and Harris	124	14.5

TABLE VII.—SURVIVAL RATES CORRELATED WITH CLINICAL STAGES (1930 TO 1950)

Stage	*No. of cases*	*Dead*	*Alive 5 years No.*	*Alive 5 years Per cent*	*Alive 10 years No.*	*Alive 10 years Per cent**
0	8	—	8	100	5	100
I	38	11	27	71.1	16	66.7
II	21	6	15	71.4	8	61.5
IIA	26	13	13	50.0	5	23.8
III	29	22	7	24.1	4	22.2
IV	37	34	3	8.1	1	3.4
IVL	43	41	2	4.7	—	—

*Based on 1930 to 1945.

TABLE VIII.—SURVIVAL RATES CORRELATED WITH HISTOLOGIC GRADING (1930 TO 1950—ALL STAGES)

Histologic grading	*No. of cases*	*Per cent 5 year survival*
High maturity		
Surgery only	32	71.9
Surgery+x-ray	11	72.7
Mid maturity		
Surgery only	29	48.3
Surgery+x-ray	14	42.9
Low maturity		
Surgery only	68	17.6
Surgery+x-ray	30	10.0

offers a poorer prognosis. Interesting is the fact that in cases in which the duration of symptoms is greater than 2 years, there is a 5 year survival greater than 50 per cent. This is similar to Figure 5 comparing staging with duration of symptoms and similar conclusions can be drawn. Allan and Hertig found a similar picture in their series and other forms of carcinoma also show a comparable observation.

Table VIII shows how histologic grading effects survival in both the groups treated with x-ray and those not given radiation. The positive correlation between degree of maturity and per cent of 5 year survival is apparent. In addition, one would expect the more anaplastic tumors to be the most radiosensitive and, therefore, to offer the better prognosis (as compared with surgery only); but such is not the case. It must be remembered also that no attempt was made here to make the groups comparable by excluding the 18 women (surgery only) dying within 30 days. Like other authors we find no correlation between histologic tvpe and radiosensitivity.

DISCUSSION AND CONCLUSIONS

The variable, but uniformly unsatisfactory, prognosis of ovarian carcinoma, as reported in the literature, demands a careful assessment of every large series of cases in order to see how methods can be improved. We believe that one step forward is the acceptance of a uniform international staging; we submit our method of clinical staging for consideration. Certain inherent advantages are noted in the staging presented: First, it follows what is considered to be the life history of the disease. Second, it correlates extremely well with prognosis. Third, unlike classifications in which operability is a factor, the surgeon's skill, experience, or daring play no role, and standardization is possible for this reason.

Our results indicate that the best therapy is hysterectomy combined with bilateral adnexal removal except in those special cases previously outlined. Unlike almost every other author, our results suggest that x-ray therapy is useful neither as a palliative instrument in prolonging life nor as a method of increasing ultimate salvage. In our series, surgery alone was at least the equal of surgery and x-ray, and possibly superior to it. Furthermore, our results with the utilization of surgery alone in cases of proved primary ovarian carcinoma compare favorably with those results which have appeared in the literature for combined surgery and postoperative irradiation.

SUMMARY

1. A review of 270 cases of primary ovarian carcinoma in the period from 1930 to 1954 is presented.

2. The patients were staged clinically into 7 groups depending upon the advancement of the disease. An explanation of the stages and their rationale was presented.

3. All cases were defined microscopically with over 95 per cent of the cases showing either serous or pseudomucinous adenocarcinoma. The more anaplastic the tumor was, the more advanced the disease, in many cases.

4. Follow-up was possible in 98.5 per cent of cases.

5. The overall uncorrected 5 year survival rate is 37.6 per cent.

6. X-ray therapy does not appear to be of value as a supplement to surgery.

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MOLLUSCUM PSEUDOCARCINOMATOSUM

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AN EDITORIAL appearing in *The Lancet* for October 17, 1953, made the following startling observation: "Squamous carcinoma of the skin was the first tumor to have its histogenesis solidly established. . . . The chain of discovery of the carcinogens was linked in the first place entirely with squamous carcinoma of the skin. The student finds here his best introduction to tumors, for these are the first he learns to recognize with any confidence. It is therefore with shock and some disbelief that clinicians and pathologists now find that a substantial portion of lesions which have been termed squamous carcinoma are in fact something quite different." The "something quite different" is molluscum pseudocarcinomatosum. It is of importance to the surgeon and pathologist for at least two reasons: (1) it is a benign lesion which does not warrant radical surgery or a guarded prognosis, both of which it frequently receives; (2) its inclusion in a series of "successfully treated" epidermoid carcinomas of the skin gives an erroneously sanguine impression regarding the true malignancy of that particular cancer.

Molluscum (sebaceum) pseudocarcinomatosum has been recognized generally and reported widely in the British literature since the description in 1936 by MacCormac and Scarff of 10 cases from the Middlesex Hospital. To our knowledge, no report on this subject appeared in the American literature until very recently. In an annotation in *The Lancet*, January 9, 1954, it was suggested that recognition of the lesion seems to follow a centrifugal pattern related to the spread of postgraduate students and medical journals from British teaching hospitals. As the result of experience at the Postgraduate Medical School of London, two of us (S. O. B. and J. A. B.) were able to make the correct preoperative diagnosis in 2 cases[1] seen in the United States and presented herewith.

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CASE REPORTS

CASE 1. A. O., a 76 year old white male, was admitted to the surgical service of the State University of Iowa Hospitals on January 4, 1955, with a polypoid lesion of the lower lip which measured 1.5 centimeters in diameter (Fig. 1). The patient, an apparently reliable witness, stated that the lesion had appeared 6 weeks prior to admission, growing during the interval to its presenting size. Grossly, it was umbilicated, firm, nontender, round, and appeared to infiltrate the lower lip. It was covered by an adherent black crust which, when removed, revealed a soft necrotic core. The edges were rolled, white, and elevated. In view of the short clinical course and gross appearance, a diagnosis of molluscum pseudocarcinomatosum was made and the lesion was excised *in toto*, including a minimal amount of adjacent normal tissue. Six weeks later, the wound was well healed, and the lip, except for a small scar, appeared normal. A nontender submental mass, 1.0 centimeter in diameter, noted at the time of admission and considered to be possibly metastatic neoplasm, no longer was palpable.

Similar histologic changes were present in 2 biopsies taken 5 days apart and in the excised specimen. The reports are combined and summarized: "Multiple sections from different areas reveal bulky, shapeless masses of mature, hyperplastic, keratinized squamous epithelium arranged in whorls and irregular papillary projections which extend outward and downward. Keratohyalin granules are conspicuous, especially in the more superficial layers where other evidence of cellular maturity is most striking. Although the lesion is well circumscribed, there is early invasion of the adjacent chronically inflamed subcutaneous tissue. There is no basal layer or basement membrane; in this junctional zone, the cells are immature, hyperchromic, moderately pleomorphic, and mitotic activity is increased. In brief, the histologic features are those of a very well differentiated low grade epidermoid carcinoma. Because of the clinical mani-

[1]Since this paper was first prepared for publication, 3 additional patients with molluscum pseudocarcinomatosum, each having clinical and pathologic manifestations peculiar to this lesion, have been studied at the University Hospitals. They have not been included in this report since insufficient time has elapsed for adequate follow-up evaluation.

festations and gross appearance, however, a diagnosis of molluscum pseudocarcinomatosum must be considered" (Figs. 2 and 3).

CASE 2. D. S., a 68 year old white male, was admitted to the hospital on March 3, 1955, stating that he first noted a "sore" on his lip 10 weeks before. During the interval until admission, it grew rapidly. He categorically denied any previous abnormality of the lip. Examination revealed an irregular, soft excrescence occupying almost half of the lower lip and covered with adherent crust and clotted blood. The lesion, which bled easily on minimal trauma, seemed to infiltrate the lip (Fig. 4). When a first biopsy failed to provide a definitive diagnosis, a second and third were obtained.

Interpretation of the first 2 biopsies was made difficult by the intense acute and chronic inflammatory reaction in and about the lesion. A histologic diagnosis of epidermoid carcinoma was made on the third biopsy: "Multiple sections from various areas reveal villous projections of irregular atypical but reasonably mature, cornifying squamous epithelial cells supported by a thin connective tissue stroma. Epithelial pearls are noted but dysplasia and moderate pleomorphism are prominent features. At the margins and base, there is no basement membrane or basal layer. Unequivocal invasion of anaplastic squamous epithelial cells into both subcutaneous tissue and muscle is conspicuous in several areas. Mitotic figures are numerous. Although the adjacent mesenchymal tissues show intense subacute and chronic inflammation, the nature and extent of epithelial invasion is greatly in excess of that which can be accounted for on the basis of irritation due to the inflammation. It is our opinion that the lesion is a low grade epidermoid carcinoma and that a diagnosis of molluscum pseudocarcinomatosum can be considered no longer" (Figs. 5 and 7).

Notwithstanding this opinion, because of the rapid growth in a short period of time as well as the gross characteristics, a clinical diagnosis of molluscum pseudocarcinomatosum was made. The lesion was treated by shaving only the polypoid portion flush with the adjacent normal lip, the treatment of choice advocated by Beare (1). The mass was vascular and friable and did not suggest carcinoma. No lymphadenopathy was noted at any time while the patient was under observation. Five weeks following surgery, the lip appeared healed completely (Fig. 8). When the patient returned 3 months after treatment, 6 weeks after his last visit, a mass, similar to, in the same location as, but smaller than that which had been present initially, was noted (Fig. 9). Because of the rapid growth during this 6 week interval and the gross appearance, it was the consensus that the lesion was recurrent molluscum pseudocarcinomatosum rather than epidermoid carcinoma. Accordingly, a simple excision was done, removing only the polypoid portion. Four months after this procedure, the wound was well healed and there was no evidence of deformity or residual or recurrent disease (Fig. 10). Histologic examination of the recurrent tumor revealed bulky, villous projections of mature cornified squamous epithelium with numerous keratin plugs, features similar to those present in the original mass.

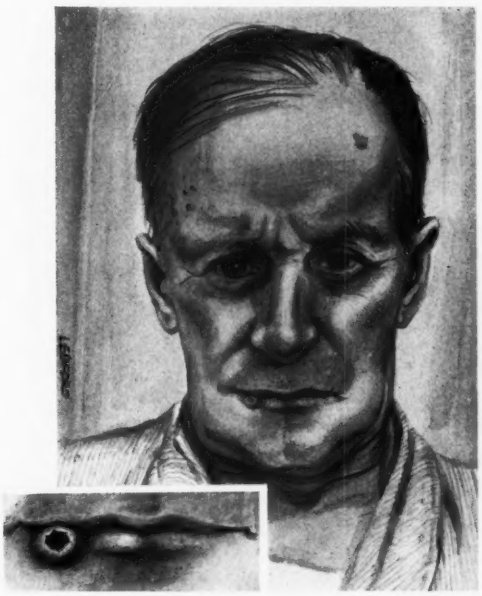

FIG. 1. Artist's drawing of molluscum pseudocarcinomatosum (Case 1).

The most striking differences were the absence of invasion, the maturity and orientation of the cells at the base of the lesion and the paucity of mitotic figures throughout. In brief, the recurrent lesion appeared as histologically benign as the original mass appeared malignant (Fig. 11).

HISTORY AND NOMENCLATURE

For at least 60 years, the literature has contained sporadic reports of skin lesions, given a variety of names, the descriptions of which strongly suggest that they were the same as or similar to that under present discussion. MacCormac and Scarff in 1936 first suggested the name "molluscum sebaceum," believing that the lesion arose from inflammation and hypertrophy in sebaceous cysts. This term has been used interchangeably with molluscum contagiosum, an entirely different skin lesion caused by a virus and containing demonstrable inclusion bodies. It now is accepted generally that molluscum pseudocarcinomatosum is of epidermal origin and probably is not derived from a sebaceous cyst. Freudenthal proposed the name "kerato-

FIG. 2.

FIG. 3.

FIG. 2. Bulky, irregular masses of squamous epithelium from midportion of lesion. Note keratin plug (Case 1).

FIG. 3. Dysplastic, pleomorphic squamous cells from near base of lesion (Case 1).

acanthoma," a rather nondescript term based on microscopic appearance and which, as Purdy points out, might be used as aptly to describe the common wart. Furthermore, "acanthoma" is employed not uncommonly by some pathologists to designate a well differentiated epidermoid carcinoma. The term "molluscum pseudocarcinomatosum," although unwieldy, emphasizes two important features, i.e., gross appearance and clinical behavior.

PATHOLOGIC FINDINGS

In the various reports in the literature, the following characteristics were ascribed to molluscum pseudocarcinomatosum.

Gross appearance. The excrescence, which is usually single but may be multiple, and which generally is found on the face but has been reported on the hands, fingers, arms, and anus, begins as a tiny painless papule which grows rapidly to achieve maximum size in 6 to 8 weeks. The size of the mature lesion varies and may involve half the lip. If the tumor is left untreated, regression usually begins in 6 to 8 weeks and often is complete in 4 to 6 months, leaving a small dimpled scar or puckered depression. When mature, the nodule is rounded or slightly flattened, hard, fixed, white with slight erythema at the base, and with a rolled edge. Nearly always at the

FIG. 4.

FIG. 5.

FIG. 4. Large polypoid ulcerated molluscum (Case 2).

FIG. 5. Shapeless masses of mature squamous epithelium from midportion of lesion (Case 2).

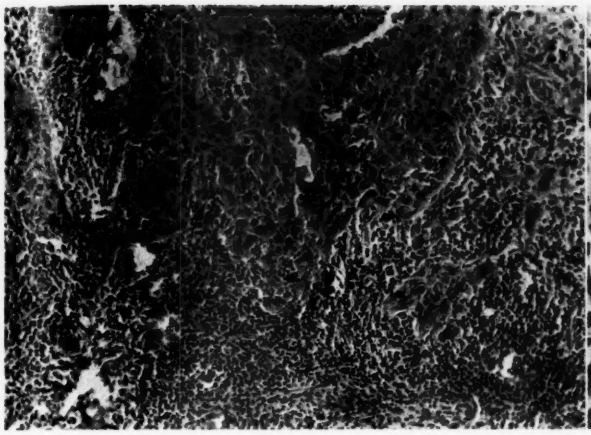

FIG. 6.

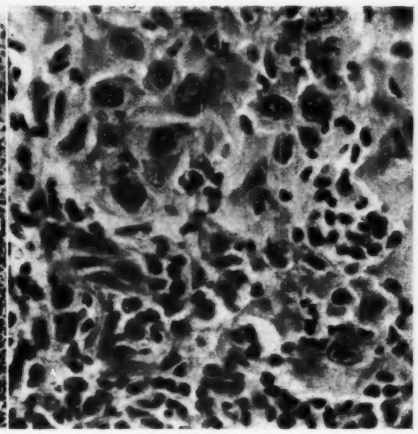

FIG. 7.

FIG. 6. Anaplastic, pleomorphic squamous cells invading subcutaneous tissue and muscle. Note intense chronic inflammatory cell infiltrate in epithelial masses and stroma (Case 2).

FIG. 7. High power magnification of Figure 6 showing greater detail of bizarre anaplastic squamous cells at invading margin (Case 2).

center of the protuberance is a crater filled with a characteristic plug of soft, friable, keratotic material covered with an adherent, blackish-brown crust. This crater is quite different from the necrotic ulcer sometimes seen with epidermoid carcinoma.

Histologic appearance. The histologic appearance varies somewhat with the age of the lesion. Younger ones may resemble, superficially, molluscum contagiosum. Most of them exhibit a central core filled with keratinous and pseudokeratinous material. The epithelium lining this crater shows marked hyperplasia and often is arranged in inverted papillary fronds. Occasionally, round, homogeneous eosinophilic masses of keratin may mimic the inclusion bodies of molluscum contagiosum. The granulosum layer is thickened. The hyperplastic, lobulated, epithelial masses which surround the crater to a variable extent usually do not show invasive changes. There is little irregularity of the arrangement, structure, or staining of the squamous cells and the nuclei are neither hyperchromatic nor enlarged. In the phase of most rapid growth, mitoses are seen. The presence of epithelial pearls and whorls is not unusual. The rete malpighii appears acanthotic and lobulated and may extend to the level of the sweat glands. These rete pegs are enveloped by normal basal cells but the basal layer may or may not be intact. Frequently, it is interrupted by an inflammatory exudate, composed of histiocytes, lymphocytes, plasma cells, and often many eosinophiles. An occasional giant cell may be seen. Thin-walled engorged blood vessels often are found near the lesion base and account for the pinkish-tinged halo sometimes seen about the tumor.

FIG. 8. Small scar, 5 weeks following surgical treatment (Case 2).

FIG. 9.

FIG. 10.

FIG. 9. Recurrence of molluscum 3 months after surgical treatment (Case 2).
FIG. 10. Small scar, 4 months after removal of recurrent lesion (Case 2).

Although the gross and many of the microscopic features enumerated were applicable to our 2 cases, certain histologic characteristics were decidedly different. The two lesions, especially the second, did exhibit changes indistinguishable from those associated with early malignancy. The most convincing was invasion, particularly striking in Case 2. But other criteria such as pleomorphism, anaplasia, increased nucleocytoplasmic ratios, multiple nucleoli, tinctorial alterations, desmoplasia, increased mitotic activity with some tripolar and "shotgun" mitoses were just as conspicuous in some areas. In short, meticulous scrutiny of multiple sections from many areas of the two lesions failed to reveal criteria sufficiently convincing to distinguish, unequivocally, molluscum pseudocarcinomatosum from a low grade, well differentiated epidermoid carcinoma. The papilliferous masses of excessively cornified squamous epithelium perhaps are more suggestive of molluscum than of epidermoid carcinoma, but to pathologists this change would be of little significance when invasion, especially into muscle, is also present. It would appear, therefore, that molluscum pseudocarcinomatosum is another example of a lesion that is biologically benign but histologically appears malignant. Extensive invasion of squamous epithelium in and about the healing bed following a transurethral prostatic resection is commonplace. Certain stages of myositis ossificans and of juvenile melanomas are further examples. In these instances, other histologic features often render the correct diagnosis possible, or, more commonly, the benign biologic behavior is recognized simply from experience. Since other helpful histologic changes were relatively unimpressive in our 2 cases, it would appear that the gross appearance and characteristic rapid growth pattern are the most definite criteria of the basic nature of the lesion. It was, in fact, these features which determined the conservative therapy in our cases. Follow-up studies have justified this form of therapy.

DISCUSSION

No specific etiologic agent or factor has been implicated conclusively. The pattern of rapid growth followed by regression is suggestive of a viral etiology, but it has not been possible to transmit the disease or isolate a virus. Beare (1), Levy and associates and Ewing have attempted without success to reproduce the lesion by intradermal injections into normal human skin of crude filtrates and suspensions. No inclusion bodies or infectious agent have been demonstrated. Marshall and Findlay were unable to inoculate successfully a chick chorio-

allantoic membrane after 3 transfers. Ereaux and associates noted the presence, after 4 or 5 days of incubation at 95 degrees F., of focal lesions on a chorioallantoic membrane which were reproduced during 5 consecutive transfers. Electron photomicrographs of the supernatant of this material produced a brick-shaped particle resembling the molluscum contagiosum virus but only one-third as large.

The so-called "multiple primary self-healing squamous cell epithelioma of the skin" of Ferguson Smith probably is molluscum pseudocarcinomatosum. Likewise, the tumor-like keratoses described by Poth on the sunburned skin of fishermen on the Gulf of Mexico also may be included. That there probably does not exist an entity such as self-healing squamous carcinoma of the skin is suggested by Fouracres and Whittick, and Brown and Fryer. It is probable that some of the spontaneous regressing tumors are, in fact, molluscum pseudocarcinomatosum, and that, as suggested by Marshall and Pepler, different clinical types may exist.

Rook and Whimster are impressed with the frequency of antecedent trauma associated with keratoacanthoma. New and Horton as well as Poth believe that sunlight is the causative agent. Sommerville and Milne point out that self-healing squamous epitheliomas of the skin occur most commonly on those portions exposed to actinic stimulation, and also suggest that there may be a genetic influence. This influence also has been emphasized by Charteris in cases of Ferguson Smith epitheliomas. Binkley and Johnson report keratoacanthomas of apparent occupational origin in workers exposed to oil or tar compounds. Beerman, however, cautions against including the oil keratoses with the lesion under discussion. With this admonition, we are in agreement. Mention already has been made of the possible etiologic role of hypertrophic and inflammatory changes in sebaceous cysts.

Up to the present time, molluscum pseudocarcinomatosum has been reported from

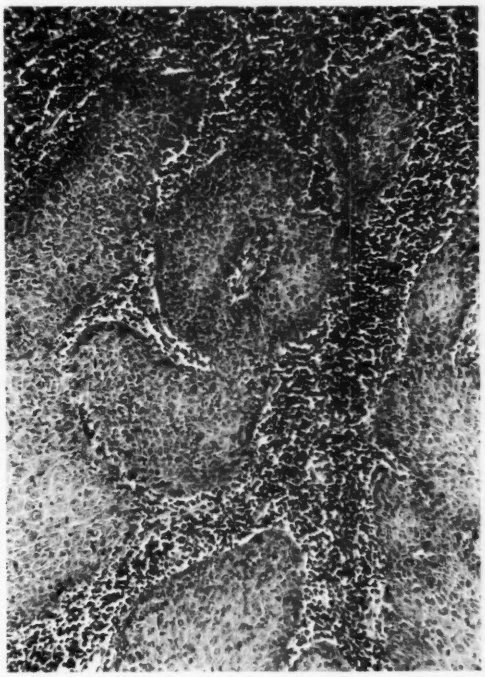

FIG. 11. Irregular, but well circumscribed masses of squamous epithelium showing intact basal layer and severe chronic inflammatory cell infiltrate in epithelial masses and stroma (Case 2).

Germany, France, The United Kingdom, New Zealand, South Africa, Canada, and very recently, the United States. It is almost certainly more common than is generally recognized. During a 38 month period, the Royal Victoria Hospital, Belfast, admitted 1 case of molluscum pseudocarcinomatosum for every 2 cases of epidermoid carcinoma of the skin. Stewart supports this observation also, stating that approximately one-third of all cases of epidermoid carcinoma of the skin are in fact molluscum. Liban and associates have reported similar findings at the Postgraduate Medical School of London. Experience at the State University of Iowa Hospitals does not appear to disclose a similar high incidence. Of all cases of epidermoid carcinoma of the skin seen during a 12 month period, only 1 in 10 presented with a clinical history of 10 weeks or less, and of these, certainly not all

could be classified as molluscum pseudocarcinomatosum. A geographic difference in the incidence of this lesion may exist. It occurs with equal incidence in males and females. To our knowledge, it never has been reported in any other than the white race. It occurs in the older age groups, chiefly the fifth to seventh decades.

TREATMENT

Simple but complete excision of the lesion, in our opinion, is the treatment of choice. It should be emphasized that wide excision customarily performed for epidermoid carcinoma is unnecessary. Shaving the polypoid portion of the lesion flush with the normal adjacent skin is less satisfactory since the possibility of recurrence may be greater. The infrequency of recurrence, however, is substantiated by the paucity of reports. Complete excision provides adequate tissue for pathologic study, and in addition, effects a good cosmetic result. The untreated molluscum pseudocarcinomatosum regresses completely, often leaving a rather ugly, puckered scar.

SUMMARY

Two cases of molluscum pseudocarcinomatosum are presented in which the correct preoperative diagnosis was made. This is an entity well recognized in Britain since 1936 but only recently noted in the American literature. Its importance to the surgeon and pathologist lies in the likelihood of confusion with epidermoid carcinoma of the skin with the inevitable consequent errors in prognosis of both conditions as well as the employment of unnecessary radical measures in the treatment of the molluscum.

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SKIN REPLACEMENT FOR SEVERE RADIATION DERMATITIS OF THE FACE

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THE PURPOSE OF THIS ARTICLE is to emphasize the seriousness of some of the types of radiation dermatitis of the face and to present two methods of handling extensive resection with immediate skin replacement in a one stage operation. The changes that occur in the postirradiated skin pass through the gamut of mild atrophy to severe fibrosis, ulceration, and cancerous degeneration. The degree and rate of degeneration depend upon the amount and type of irradiation used, the time interval following therapy, and the sensitivity of the skin. Keratoses, irradiation ulcers, and localized basal cell cancers comprise the vast majority of the late complications of this condition. They are successfully treated by electrodesiccation or surgical removal and repair. Occasionally, sarcoma arises in the irradiated fibrous tissue, and it is successfully treated by surgical excision and repair. The serious aspects of this condition are associated with development of primary squamous cell cancer or the development of squamous cell cancers in radiation ulcers. When this tendency repeats itself or becomes widespread on the face, the serious danger of the local disease is compounded by the potential for local or generalized metastases.

This latter situation demands aggressive and definitive therapy. The most conclusive treatment is the excision of all of the skin involved in the process and the replacement with either a free, thick-split skin graft or rotated pedicle flap. In the past, the hazards and failures associated with full face replacement were complicated with infection and the difficulty in procuring satisfactory epithelial covering. Biotherapy and technical improvements have mitigated these dangers. A one stage skin replacement of the face can now be carried out by application of a free graft or pedicle flap with excellent expectation of cure of the disease and esthetic improvement.

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INDICATIONS

Indications for extensive replacement of the skin of the face in respect to x-ray dermatitis, ulceration, and cancer are associated with active degeneration of the postirradiated skin which cannot be controlled by a less formidable technique. Obviously, not all individuals with x-ray dermatitis of the face are candidates for this type of surgery. Indeed, few are. The treatment is governed by the clinical course of the disease. Localized radiation dermatitis is a limited problem, usually cured by local excision and repair. Even the diffuse radiation dermatitis may remain dormant or manifest minimal degeneration throughout the patient's entire life. When these are the circumstances, minimal local excision ordinarily suffices to control the condition. However, when diffuse radiation dermatitis degenerates into multiple areas of squamous cell cancer, the degenerating skin covering should be totally removed and appropriate replacement substituted. Procrastination at this point may cost the patient his life by spread of the cancer to regional and systemic areas.

It is most important to carefully evaluate the psychologic aspects of the patient. This is particularly true in the female group from 20 to 40 years of age. Their lives have been vastly complicated by the inconvenience and threat associated with this condition. Depression, anxiety, frustration, and hostil-

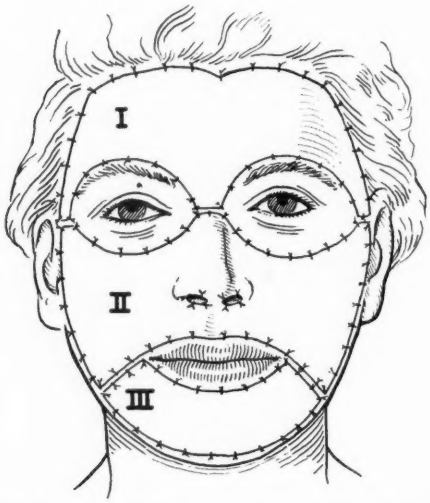

FIG. 1. Replacement of skin of face, exclusive of eyelids, with 3 free, thick-split skin grafts. Microstomia and ectropion are not complicating factors.

ity are common manifestations and require psychiatric assistance. The hostility engendered for the individual who arranged for or gave the initial irradiation, usually the parent or therapist, may be directed toward the plastic surgeon after the completion of the surgery. Depressions may be associated with suicidal tendencies. Males in all age groups and females in the older age groups (40 to 60 years of age) accept the hardships of the complications with more equanimity, but the psychologic burden is a heavy one in all age groups and cannot be minimized.

The indications may be listed as follows: (1) postirradiation dermatitis and ulceration with a high potential for squamous cell cancer; (2) multiple and repetitive squamous cell cancers of the face; (3) disseminated interepithelial basal cell cancer. (Extensive burns of the face and extensive scar tissue contraction of the face may, in general, be handled in a similar manner but will not be discussed in this article.)

Irradiation was given extensively by untrained individuals in the past for the treatment of acne, excessive hair, eczema, and dermatitis of the face, with a resultant large percentage of late postirradiation dermatitis and ulceration. A full grown respect for the effects of irradiation has increased the cautious and judicious aspects of its use today. Postirradiation dermatitis and ulceration may occur from 5 to 25 years after superficial or deep irradiation has been applied. The characteristic late postirradiation changes are atrophy of the skin, subcutaneous tissue and muscle, fibrosis in the subcutaneous tissue, telangiectasia in the subepithelial bed, and a mottled, diffuse pigmentation of the skin.

If the postirradiated skin is adequately protected from the trauma of sunlight, weather, excessive washing and drying, and concomitantly nourished with a protective cream it may successfully carry out its physiologic functions as a covering organ for the duration of the patient's life. If it is possible to accomplish this, it is usually the happiest solution for all the parties concerned. This, unfortunately, is not always possible, and the disease progresses to the formation of keratoses and ulceration. In the beginning, blemishes appear and disappear spontane-

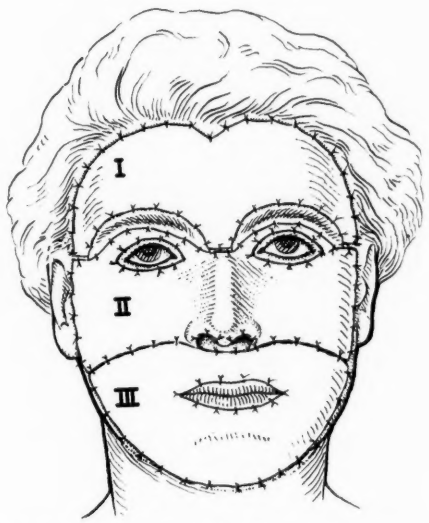

FIG. 2. Replacement of skin of face, including eyelids, with 3 free, thick-split skin grafts. The tendency toward ectropion is minimized by this graft slitting technique. The tendency toward microstomia is increased.

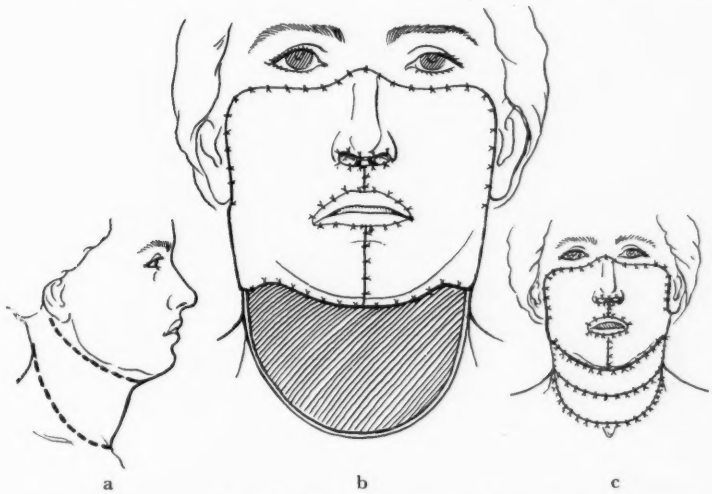

FIG. 3. Replacement of skin of face by rotating neck flaps. These flaps are cut according to measurements of the face wound. The donor area is dressed with 1 or 2 free skin grafts.

ously, but eventually persist in the formation of nodules or ulcerations that gradually increase in size. In the early stages of cancerous degeneration the lesions are small and discrete.

The basal cell cancer, which is the most common variety of complicating malignant tumor, is locally invasive and will destroy large areas of the face if not properly treated. Fibrosarcomatous proliferation is a slow growing solid tumor with little tendency to metastasize. A squamous cell cancer readily metastasizes and greatly increases the seriousness of the prognosis in these cases. A preliminary analysis of these factors usually reveals that the degree of involvement and the intensity of degeneration are well within the patient's emotional capacity to accept repeated minimal local excisions. This may lead to two or three minor operations a year for the duration of the patient's life. In some instances, the intensity of cancerous degeneration accelerates, and a more aggressive form of therapy is required to control the disease. In many patients, the depression associated with the realization of repeated operations and the unending threat of recurrent cancer in the irradiated skin compels a more definitive type of treatment. It is under these special circumstances and after careful evaluation that excision of the irradiated skin of the face and immediate replacement is indicated.

The type of replacement depends upon the position and size of the area to be grafted and the availability of neck skin for transplantation. The areas most heavily involved in the radiation degeneration after the treatment of acne, excessive hair, and dermatitis are the nose, cheeks, lips, and chin. The brow is often not seriously involved. The eyelids are almost always protected with lead shields during exposure to x-ray and are not involved. These latter two facts greatly simplify the replacement techniques. The problem, therefore, in most instances, resolves itself into a replacement of skin of the cheeks, nose, lips, and chin. Under these conditions, the skin of the neck can be transposed as a pedicle flap to cover these sites in a one stage procedure.

In some individuals whose original skin disease was eczema, the neck may also have been previously treated by irradiation and is unusable as tissue for transplantation. When this condition prevails the transplan-

a b c

FIG. 4. a, X-ray dermatitis, ulceration, and cancer of the middle and lower third of face replaced in a one stage operation by free split skin grafting. b, One week postoperative. c, Eleven months postoperative. The esthetic effect will continue to improve and can be further aided by tattooing and additional makeup.

tation of free thick-split skin grafts from non-hair-bearing areas is the method of choice. This resurfacing technique should be carried out as a one stage procedure.

When it has been necessary to resect not only the skin of the face but that of the nose, lips, and maxillae as well, pedicle tissue replacement is essential. Neck pedicles are satisfactory but not always available because of scar formation from previous surgery or intrinsic disease. The most satisfactory technique under these circumstances is the use of a scalp or scalp-brow pedicle flap transposed onto the face in a one stage procedure.

The eyelids and lips present special problems. When the eyelids are involved in radiation degeneration or in disseminated intraepithelial basal cell cancer (Bowen's disease), reconstruction may be necessary and special precautions must be exercised to minimize ectropion. When the cancer has invaded the lips, reconstruction of the upper and lower lips may need to be performed during the skin replacement operation.

In the more complicated and serious problems of multiple deeply infiltrating squamous cell cancers developing in x-ray ulcerations of the face, one must not only be prepared to treat the local malignant lesion more aggressively, but also to cope with cervical metastases. Locally on the face this may require partial resection of the upper or lower oral commissure, a portion of the cheek, nose, mandible, maxilla, and orbital contents, in addition to the epithelial covering of the remainder of the face. If there is cervical metastasis a block dissection of the neck is carried out simultaneously with these techniques described; the skin of the neck cannot be used for pedicle rotation and free skin grafting to the face is indicated.

ROTATING PEDICLE NECK FLAPS

The procedure of choice for resurfacing the face is rotated pedicle neck flaps. This technique not only presents the possibility of a complete cure of the disease but also a striking improvement in esthetic appearance. The advantages of the pedicle flap over other techniques are: (1) It is a one stage operation. (2) The probability of a complete "take" is high. (3) The replacement is accomplished with the normal full thickness skin and subcutaneous tissue. (4) The color and quality of the transplant are excellent. (5) There is little contraction.

The difficulties of the pedicle flap are that they create another donor area in the neck

which must be covered with a free split skin graft. It is also necessary to perform minor touch-ups about the nose after the flaps are well taken. These disadvantages do not diminish their excellence.

The basic surgical technique consists of the complete removal of the skin and subcutaneous tissue where indicated on the cheeks, nose, lips, and chin. After complete hemostasis, the skin and platysmal muscle of the neck are raised from the chin to the clavicles and the sternum (12 to 15 cm. depending upon recipient area requirements). With bilateral posterior superior neck pedicles attached these flaps are raised individually or as a single flap in reverse visor fashion onto the face. The external nares and oral opening are modelled and the flaps sutured into position. A free thick-split skin graft is sutured into the donor area on the neck. A supportive dressing is applied. Feeding is accomplished per Levin tube. Ample biotherapy is administered. A tracheostomy is not required.

It is always necessary to carry out refinements after the wound has healed. These consist of removing the excessive tissue over the nose (platysmal muscle and subcutaneous fat) to give it better shape. Minimal composite grafts may improve the alar rims. Hair may appear on the nose in males, and this can be depilated. If the patient desires, the free skin graft on the neck may be replaced at a later date by a rotating chest flap in males, or a rotating back flap in females. The face has good form, color, and movement after 3 or 4 weeks, and the result is gratifying.

a b

FIG. 5. a, Postirradiation dermatitis, ulceration, and cancer of the middle and lower third of face replaced in a one stage operation by rotating neck flaps onto the face. b, Nine months after face graft. (Bilateral composite grafts were implanted at the alae of the nose 2 months prior to this photograph.) Note excellent skin matching and facial contour. Touch-ups about upper lip and nose will give additional improvement.

a b

FIG. 6. a, Multiple squamous and basal cell cancers involve skin of face, nose, upper lip, and lower lip with infiltration into maxillae and palate. b, The skin of the face has been replaced. A new nose, upper lip, and middle third of face were made from a scalp flap. Composite grafts are in the position of the alae of the nose.

FREE SKIN GRAFTS

Unfortunately, pedicle neck grafts cannot always be carried out. If the neck has been exposed to irradiation or involved with cancer it is unsatisfactory for a pedicle transfer and there is no alternative except to use free grafts or scalp pedicle flaps if it is desired to perform a one stage procedure. There are no advantages to the use of the free graft or scalp flap over the use of neck pedicle flaps. However, in comparison with other multiple stage techniques of resurfacing, they have the advantages of cure of the disease and an improvement in facial esthetics in a single operation.

The inconveniences and disadvantages of free skin grafting on the face are associated with contraction of the graft which always takes place to some degree. It may vary from 10 to 50 per cent of the square surface

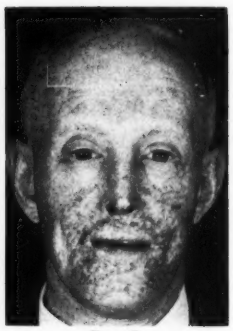

FIG. 7.

FIG. 8.

FIG. 7. Postirradiation dermatitis under control at the present time, requiring intermittent local excisions of basal cell cancers. This condition may become serious.

FIG. 8. Multiple repetitive squamous cell cancers following irradiation for acne in childhood, eventually metastasized to the neck bilaterally and to the lungs, causing death.

of the graft. It is impossible to predict in advance how much contraction will occur. This contraction is the result of scar tissue and fibrosis about the suture line and on the base of the graft. It takes at least a year for the graft to soften and to become relatively natural in quality. The color and quality of the free graft are never equal to that of natural skin. The grafted skin is usually thinner, whiter, and stiffer. However, with the aid of tattooing or some other type of camouflage, such as covermark or makeup, an acceptable esthetic result is easily attained. There is often a temporary microstomia, particularly in individuals whose oral commissures have been resected. There is almost always some degree of ectropion if the covering over the eyelids is excised along with the skin of the face. This complication has been minimized by an improvement in the grafting technique.

The technique of free skin grafting to the face consists of the complete removal of the cancerous and degenerating epithelium and subcutaneous tissue. Hemostasis must be complete. Thick-split free skin grafts are procured from hairless donor areas of the body with the Padgett dermatome. If the eyelids are not involved, one section of skin is used to cover the brow, another for the cheeks, nose, and upper lid, and a third for the chin and lower lip. If the eyelids are involved one section of skin is used for the brow, another for the cheeks, eyelids, and nose, and a third for the lower cheek, chin, and lips. The grafts are "pie-crusted" and sutured to the face securely with fine silk. Special slits are made in the grafts for the eyelids and oral commissures, care being taken to minimize ectropion and microstomia. A pressure dressing is applied, ample biotherapy is administered, and the patient is fed per Levin tube. Ectropion is minimized by the latter technique of slitting the graft about the eyelids. As this area heals, all forces of contraction work against the development of ectropion. If it should develop, a full thickness skin graft will correct it. After the stiffness and contraction have disappeared from the face and color improvement has been accomplished by tattooing or makeup, the therapeutic and functional results amply justify the effort.

SCALP FLAPS

The scalp flap is a vigorous biologic flap that can be transposed without delay. Its pedicles at the zygoma include the superficial temporal arteries. The required replacement on the face is tailored generously on the scalp, according to pattern. The scalp donor area is covered with a free split skin graft after the pedicle flap has been pulled down like a visor to cover the deficiencies in the face. If flap lining is required to substitute for mucous membrane surface, one can include the brow (hairless), pincushioned back on itself or a free graft on the inner surface of the pedicle. If bone implantation or a prosthesis are to be used at a later date, the flap should be tailored generously to accommodate this third dimensional alteration. The flaps can be released in 2 to 3 weeks. Because this flap is ordinarily a hair-bearing one, it is only adaptable to males. The hair in the male may be used as a camouflage in the form of a mustache to assist in the esthetic improvement. If the flap includes the nose, the hair may be removed by depilation.

When females require flap replacement and the neck is not available, tissue must be transposed in multiple stage operations from the back or abdomen. The scalp flap is quite stiff and nonelastic in comparison with other body tissue flaps, but this is not undesirable, particularly in total reconstruction about the lips.

SUMMARY AND CONCLUSIONS

Attention is drawn to the hazards of late radiation degeneration with cancerous formation. The vast majority of these conditions are best handled by diligent care and protection of the skin. Local excisions and desiccations are carried out as the clinical course dictates. The seriousness of multiple or repetitive squamous cell cancers and degeneration in postirradiation dermatitis is emphasized. Three surgical methods of treatment are described. All are single stage operations designed to replace the epithelial covering of the face by either pedicle flaps rotated from the neck and scalp, or the application of free skin grafts. The pedicle flaps from the neck are superior to the free skin graft and scalp flap, but unfortunately in some circumstances the skin of the neck has been affected by radiation degeneration, scarring, cancer, or metastases and is not satisfactory for transfer. Free skin grafts are used in these instances. The scalp pedicle visor flap is often of great advantage in the male in the presence of full thickness loss of soft tissue and bony architecture about the face.

Psychologic aspects of these conditions merit careful preoperative evaluation. Insecurity, anxiety, hostility, and depression are common disorders and may assume acute proportions. When radical surgery is necessary, psychiatric help may prevent unnecessary depression of the patient.

Need for minor touch-ups about the nose and eyelids must be expected in some instances, but the curative and esthetic results for these most perplexing and serious problems are gratifying.

EVALUATION OF SPLENECTOMY IN THE TREATMENT OF EGYPTIAN SPLENOMEGALY (FIBROCONGESTIVE SPLENOMEGALY)

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EGYPTIAN SPLENOMEGALY can be defined as a clinical entity endemic in the Nile delta of Egypt, characterized by splenomegaly, cirrhosis, signs of portal hypertension, anemia, leucopenia, and, as a rule, demonstrable Schistosoma mansoni ova in the feces. The histologic features of the spleen are identical with those of fibrocongestive splenomegaly (9). There has been much controversy concerning the role of schistosomiasis in the production of this clinical entity, and it is the general consensus that schistosomiasis is the major etiologic factor. It is our belief that the hepatosplenic disease present in the Egyptian patients is primarily a result of schistosomal thrombopylephlebitis of the liver due to dead adult parasites and live ova; however, there are other important factors which have been learned in a study of the pathology and the pathogenesis of this disease (9).

Splenectomy has been used in the treatment of Egyptian splenomegaly for many years, even though there has been some question regarding its value both in this entity and in chronic congestive splenomegaly due to other causes. At present it is the consensus among the Egyptians that splenectomy is beneficial only in selected cases. At the American Mission Hospital at Tanta, Egypt, however, where 255 splenectomies have been performed, the conclusion has been reached that splenectomy is more effective than is generally believed and should be the treatment of choice for all patients with Egyptian splenomegaly who are reasonably fair operative risks.

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This article has been approved for publication by the Office of the Surgeon General and Bureau of Medicine and Surgery, Navy Department.

It is the purpose of this report to present clinical and laboratory evidence of the value of splenectomy in Egyptian splenomegaly in the Egyptian fellahs (peasants) who were treated at the American Mission Hospital from 1947 through 1953.

GENERAL CONSIDERATIONS

The 135 patients on whom this study was conducted were divided into two groups on the basis of time of operation and extent of the clinical study. Group A consists of 49 cases in which splenectomy was performed during the year of 1953 and in which the signs and symptoms were subjected to analysis. Group B is made up of 86 cases in which splenectomy was performed from 1947 through 1952. Postoperative clinical examinations were made, but the signs and symptoms were not analyzed. Patients of both groups were first seen in the outpatient clinic of the American Mission Hospital. The occupation in every instance was farming. Generally, the patients' complaints were "heaviness in the abdomen," recurrent abdominal pain, weakness, and easy fatigability which severely inhibited their

ability to work in the fields. The patients were selected for splenectomy on the basis of the following criteria: (1) abdominal symptoms, weakness, and fatigue; (2) moderate to severe splenomegaly (Fig. 1); (3) desire to be hospitalized and willingness to undergo splenectomy.

The sex and age distribution of the patients in group A is summarized in Table I, the incidence of clinical signs and symptoms in Table II, and the results of the laboratory examinations performed before and several months after splenectomy in Table III.

Following the completion of the initial clinical and laboratory studies splenectomy was performed, and during the procedure a wedge of liver tissue was removed for histopathologic study. The histopathologic studies on the liver tissue and spleens will be described in a subsequent report (9).

FIG. 1. Case 23. Egyptian adult male with Egyptian splenomegaly and hepatomegaly.

SURGICAL TECHNIQUE OF SPLENECTOMY IN EGYPTIAN SPLENOMEGALY

The surgical technique used in this series was evolved at the American Mission Hospital over a period of 20 years, during which splenectomy was performed on more than 500 patients with Egyptian splenomegaly. This experience has demonstrated that there is no standard technique which is applicable to every case. In addition to the greatly enlarged spleen, distended venous collateral channels are frequently present and some of them traverse the dense adhesions which have formed between both the splenic capsule and omentum and the parietal peritoneum and omentum. Schistosomal tubercles are frequently observed on the serosa of the cecum, the sigmoid colon, and the appendix (Figs. 3 and 4).

For the majority of patients the incision used is the upper midline, beginning at the ensiform cartilage and extending down to the umbilicus. In cases in which the spleen extends down to the left iliac crest, the incision is continued to the left of the umbilicus as far down as is necessary.

After the abdomen is opened, a survey is made of the omental and splenic adhesions, the venous collateral channels and the ascites. The splenic capsular adhesions to the parietal peritoneum are usually very vascular, but they may be separated by blunt dissection if the operator is cautious. The bleeding at the site of the detached adhesions can be controlled by warm, wet packs, which are gently pressed into the splenic fossa while the splenic pedicle is ligated. In some cases it is possible to open the gastrocolic omentum, thus exposing the large distended vessels of the splenic pedicle. It is advantageous to ligate the splenic artery before the spleen is mobilized, but because of the position and shortness of the pedicle it frequently is impossible to do so; therefore, it is necessary to ligate the entire pedicle and then ligate the individual vessels after the spleen is removed.

The short gastric arteries are often prominent and may be torn when delivery of the spleen is attempted; therefore they should be ligated before the spleen is delivered. After removal of the spleen, the stomach must be carefully examined for bleeding

TABLE I.—AGE AND SEX OF PATIENTS IN GROUP A

			Age, years		
Patients	*No.*	*Per cent*	*Mean*	*Median*	*Range*
Total	49	100.	31	30	39(11–50)
Male	40	82.	30	30	39(11–50)
Female	9	18.	34	35	18(22–40)

FIG. 2. Twenty-eight year old Egyptian female with Egyptian splenomegaly. Marked distention of abdominal veins demonstrated by infra-red photography.

from any denuded areas along the greater curvature. At the same time, the inferior surface of the left leaf of the diaphragm should be inspected for bleeding. After hemostasis of the splenic fossa and the gastrosplenic ligament is accomplished, the defect in the omentum is closed and its attachment to the greater curvature of the stomach re-established.

No thrombi or other gross pathologic changes were observed in the splenic veins during the course of the splenectomies, nor did superficial examination of the portal veins reveal any abnormalities. In several instances measurement of the portal venous pressure was attempted, but in only 1 was the attempt successful. The reading in this case exceeded 500 millimeters of water. The failure in other cases was due primarily to the bleeding which had resulted from the introduction of the needle into the splenic vein.

The omentum is often found to be adherent to the left lateral parietal peritoneum below the inferior pole of the spleen (Fig. 4). Large venous collateral channels frequently traverse these omental adhesions, and it has been found that it is neither necessary nor desirable to disturb them. The vessels in the falciform ligament (paraumbilical vein) are also left undisturbed when possible.

Due to the shortage of suitable blood donors, only 1 or 2 pints of blood were available during any of these splenectomies. As a supplement, the splenic blood was used for transfusion in most cases. In this procedure, immediately after the spleen is removed, it is inverted over a large sterile container of sodium citrate, and the clamps on the splenic vessels are removed. The quantity of blood obtained in this manner varies from 500 to 1,000 cubic centimeters. The blood is filtered through sterile gauze and transfused to the patient. No reaction from the transfusion of this splenic blood has been observed.

Following the splenectomy, a wedge of tissue for histopathologic study is removed from the anterior margin of the right lobe of the liver. The abdominal wall is then closed in layers by the use of interrupted silk sutures.

FIG. 3. The spleen (weight, 900 grams) from patient with Egyptian splenomegaly. Enlargement of the spleen is demonstrated, and extensive perisplenitis (Zuckergus) is present.

RESULTS

Physical signs and symptomatology. Table II presents the incidence of the major signs and symptoms of patients in group A. Enlargement of the liver was noted in 86 per cent of the 49 patients. The average distance of the edge of the liver from the right costal margin (midclavicular line) was 6 centimeters. Splenomegaly was present in all of the patients. The average distance between the left costal margin (midclavicular line) and the lower pole of the spleen was 11 centimeters (Fig. 1).

A dermatitis characteristic of pellagra was noticed in 12 per cent of the patients. No other clinical signs of vitamin deficiency were observed.

The liver was tender to palpation in 72 per cent of the 43 patients for whom this specific sign was recorded.

According to the case histories the most prevalent symptoms were pain or "heaviness" in the region of the spleen, recurrent abdominal pain or cramps, weakness and easy fatigability, diarrhea, and hematuria. The duration of symptoms was found to vary from 2 months to over 10 years; however, it is difficult to evaluate the reliability of the patients' statements because the educational level of the Egyptian peasants who made up the group is very low. The most disabling symptom was the pain or "heaviness" which was present in 91 per cent of the patients. This symptom prevented or greatly restricted performance of their daily labor, such as hoeing or picking cotton. Weakness and easy fatigability were other major factors which restricted the ability to work. The history of hematuria, given by 38 per cent of the 37 patients questioned in this regard, is suggestive of Schistosoma haematobium involvement of the genitourinary tract, since this species is also indigenous to the Nile delta.

The incidence of clinical signs of portal hypertension in this group was: splenomegaly, 100 per cent; ascites, 26 per cent; distended veins, skin of abdomen (Fig. 2), 8 per cent.

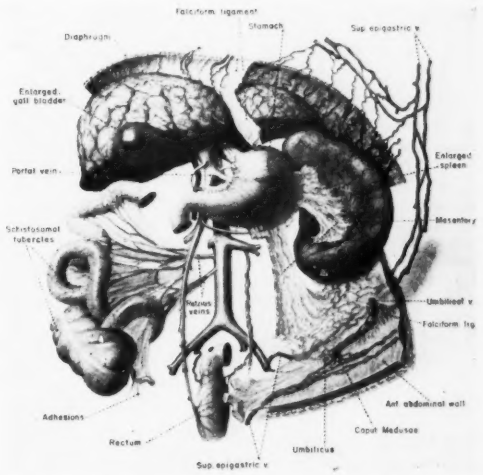

FIG. 4. Diagrammatic representation of the gross appearance of the liver and spleen and the major venous collateral channels encountered during splenectomy in a patient with Egyptian splenomegaly. The most prominent venous channels noted were: (a) those between the splenic capsule and the lateral abdominal wall and the diaphragm, (b) those within the anterior abdominal wall around the umbilicus extending into the falciform ligament, (c) those within the omentum extending through adhesions into the anterior abdominal wall.

Hematemesis, due to bleeding from esophageal varices, is considered one of the major problems in portal hypertension, regardless of the etiology. Only 2 patients, however, gave a history of hematemesis.

A correlation between the degree of liver enlargement and the degree of enlargement of the spleen could not be established.

No other clinical signs of liver disease were noted in any of the patients.

Clinical status of patients (group A) following splenectomy. Table IV summarizes the status of the patients following splenectomy. The average time interval between splenectomy and the latest clinical follow-up examination was 5.4 months for the group (63 per cent) who had recovered and returned to work, and 3.7 months for the group (23 per cent) who in spite of apparent clinical recovery had not been able to resume work. Table IV shows that 63 per cent of the patients had resumed full-time work

TABLE II.—SUMMARY OF MAJOR SYMPTOMS AND SIGNS IN GROUP A

Symptoms and signs	*No. with specific data recorded*	*Per cent with symptom or sign*
Splenic pain or "heaviness"	46	91
Abdominal pain	43	74
Weakness	41	78
Diarrhea	38	61
Hematuria	37	38
Hematemesis	49	4
Liver enlarged	49	86
Spleen enlarged	49	100
Tenderness of liver	43	72
Pellagrous dermatitis	49	12
Ascites	49	26
Distended veins, skin of abdomen	49	8

in the fields, whereas, prior to splenectomy, the useful activity of all these patients had been restricted or prevented by the disease. Twenty-three per cent of the patients whose spleens had been removed were without complaints but had been unable to resume full-time work as farmers.

The liver was no longer palpable in 6 patients in whom it had been enlarged before splenectomy, nor was tenderness of the liver noted in 18 patients in whom it had been present preoperatively. Ascites was no longer evident in 23 of the 29 patients in whom it had been present prior to splenectomy. No patient gave a history of hematemesis after splenectomy.

Hospital and late mortality. The hospital mortality in group A was 8 per cent. One patient (Case 14) died 6 hours following splenectomy, death being attributed to postoperative shock. Shock developed during the operation in Case 38, and the patient died before the splenectomy could be completed. Three late deaths (6 per cent) occurred in this series. Summaries are given in Table V.

Data from group B. Although the signs and symptoms of the 86 patients in group B were not analyzed as were those of group A, it was noted that the major difficulty which brought the patients of group B to the hospital was the same as that of group A—partial or complete inability to work.

Table VI summarizes the results of the postsplenectomy clinical examination of the patients in this group. It will be noted that 78 per cent of the patients had recovered sufficiently to resume full time work. Only 13 per cent were unable to work or were able to work only part time. The hospital mortality rate in group B was 9 per cent, as was also the late mortality rate.

The time interval between splenectomy and the most recent clinical examination of the patients in group B was: 5 to 6 years in 18 patients; 4 to 5 in 10; 3 to 4 in 10; 2 to 3 in 11; 1 to 2 in 22; and less than 1 year in 5 patients. One half of these patients were examined from 3 to 6 years following splenectomy.

LABORATORY STUDIES (GROUP A)[1]

Hematologic data. Table III and Figures 5, 6, and 7 summarize the hematologic studies. Hematologic examinations were performed on 40 patients both before and after splenectomy. A great majority of the patients showed leucopenia, eosinophilia, and moderate anemia before removal of the spleen. At the time of the follow-up examination, no patients exhibited leucopenia and the majority had a slight leucocytosis. The hemoglobin and hematocrit determinations and the erythrocyte counts showed a statistically reliable mean increase after splenectomy (Figs. 5, 6, and 7). The erythrocyte sedimentation rate had been elevated in all but 1 patient prior to splenectomy.

Liver function tests. Table III and Figure 8 summarize the results of the liver function test before and after splenectomy. Bromsulfalein clearance, thymol turbidity, and cephalin-cholesterol flocculation tests were abnormal before splenectomy in the majority of the patients, indicating hepatocellular damage. There was a reliable decrease in the bromsulfalein clearance and the thymol turbidity postoperatively, although none of the determinations reverted to normal. On the other hand, almost one-half of the patients (29) with abnormal cephalin-cholesterol flocculation tests before splenectomy showed normal results after the spleen had

[1]Probability values of .05 were accepted as evidence of a reliable increase or decrease between the presplenectomy and corresponding postsplenectomy determination.

TABLE III.—SUMMARY OF LABORATORY DATA IN GROUP A

Laboratory determinations	*Normal values*	*Mean*		*No. of patients*
		Pre-splenectomy	*Post-splenectomy**	
White blood cell count, mm.3	5–10,000	3,907	10,952	40
Red blood cell count, 10^6/mm.3	4.2–6.2	3.6	3.9	40
Hemoglobin, gm./100 ml.	12–18	9.6	11.1	40
Hematocrit, per cent	37–54	38.2	48.7	40
Sedimentation rate (Cutler method), mm./hr.	0–10	23.0	Not done	42
Serum bilirubin (Malloy-Evelyn method), mgm. per cent	0–1	0.69	0.53	40
Thymol turbidity, T. units	.53–5.25	7.75	6.98	40
Bromsulfalein (5 mgm./kgm. bw. dosage), mgm. per cent	Less than 5	8.12	6.93	38
Total blood protein, gm./100 ml.	6–8	7.30	6.76	27
Hypoproteinemia (below 6 gm. per cent), per cent	—	0	4	27
Hyperglobulinemia (above 3 gm. per cent), per cent	—	81	67	27
Cephalin flocculation (Hanger method), per cent above 2+	1+–2+	76	40	38
Presence of:				
Schistosoma ova (feces), per cent	—	53	—	49
Schistosoma ova (urine), per cent	—	22	—	49
Schistosoma ova (scrapings of rectal mucosa), per cent	—	32	—	19

*Mean interval between presplenectomy and postsplenectomy, 4 months.

been removed (14) (Fig. 8). The entire battery of liver function tests was normal in 2 patients following splenectomy, but the bromsulfalein clearance tests had been normal before the spleen was removed.

Five patients demonstrated a slight hyperbilirubinemia preoperatively, and in 2 the bilirubin level reverted to normal after operation.

Of the 27 patients on whom albumin-globulin determinations were made both before and after splenectomy, 81 per cent had shown hyperglobulinemia before splenectomy. There was a reliable mean decrease in the globulin determination in 18 of the 27 patients (67 per cent). Hyperproteinemia had been observed in 6 of these patients (22 per cent) before splenectomy and hypoproteinemia (below 6 grams per cent) in none. Seven of the 13 patients in whom there had been reversal of the albumin-globulin ratio before splenectomy had a normal albumin-globulin ratio after splenectomy. Only 3 patients (11 per cent) were hypoalbuminemic (below 3 gm. per cent) before splenectomy. After the operation the albumin determination rose to normal in 2, while in the third it remained subnormal.

Incidence of Schistosoma ova in the feces and urine. Fifty-three per cent of the 49 patients were found to have Schistosoma ova (type unspecified) in the feces upon direct microscopic examination. In 22 of the 49 patients Schistosoma ova (type unspecified) were demonstrated in the urine by concentration technique of the 24 hour sample.

Examination of the rectal mucosa for Schistosoma ova. Scrapings of the rectal mucosa were obtained from 19 patients during proctoscopic examination and were examined by direct microscopy. Schistosoma ova (type unspecified) were present in 32 per cent.

The presence of other ova and parasites in the stools of these patients was not recorded. It has been reported by Chandler, however, that ancylostomiasis is present in 10 to 25 per cent of the Egyptian fellahs. According to Lawless practically 100 per cent of the older children and adults harbor Endamoeba histolytica.

DISCUSSION

The most significant indication of the clinical improvement following splenectomy was the ability of 63 per cent of the inca-

TABLE IV.—RESULTS OF POSTSPLENECTOMY CLINICAL EXAMINATION IN GROUP A

Status	*No.*	*Per cent*	*Average duration post-splenectomy, mos.*
Total	49	100	—
Recovered, working	31	63	5.4
Recovered, not working	11	23	3.7
Operative deaths	2	4	—
Late deaths	5	10	—

pacitated patients of group A and 78 per cent of those of group B to resume complete physical activity (Tables IV and VI).

The poor economic status of the Egyptian peasant makes it absolutely necessary that he be capable of working full time. (Twenty-three per cent of the patients in group A and 13 per cent in group B had not returned to work full time at the time of the follow-up examination.) The average interval between splenectomy and follow-up examination for patients of group A who had returned to work was 5.4 months while the average for the nonworking group was 3.7 months. It should be noted, however, that several were examined only a few weeks after splenectomy, although the average interval between the operation and follow-up examination for the entire group was 4 months.

Clinical improvement in the status of the liver disease, indicated by the disappearance of enlargement and tenderness of the liver, was noted in some of the patients after splenectomy. Ascites was no longer seen in 23 of the 29 patients in whom it had been present before the spleen was removed.

None of the patients had episodes of hematemesis following splenectomy, but only 2 patients had given a history of it before the operation. As mentioned previously, hematemesis is considered to be the major problem in portal hypertension. However, its relative infrequency in Egyptian splenomegaly has been observed by one of us (H.S.H.) for many years. Before this phenomenon can be explained, direct observations of the esophagus must be made by esophagoscopy in a number of patients with Egyptian splenomegaly.

Palmer and Jahnke, in a study of 17 Puerto Rican soldiers with schistosomiasis and portal hypertension, noted esophageal varices in 7 patients by direct observation. Six of these patients reported previous episodes of hematemesis.

A significant improvement in the hemoglobin and hematocrit determinations and the leucocyte and erythrocyte counts was observed following splenectomy (Figs. 5, 6, and 7). This improvement is probably due to two factors: first, the elimination of a hypersplenic factor by removal of the spleen, a subject that has been reviewed recently by Dameshek; second, the improvement in the general well-being of the majority of the patients leading to increased appetite, better economic status through ability to work full time, and ultimately better nutrition.

Vilter and co-workers, on the basis of a nutritional survey in Egypt, found that the natives in the samples of the population which they studied had definite hypochromic anemia, due primarily to blood loss from intestinal parasitism and an inadequate intake of dietary iron. Because of these indigenous factors, it is difficult to evaluate accurately the effect of splenectomy or better nutrition on these patients.

The liver function tests following splenectomy were indicative of improved liver function in some patients. This observation suggests that splenectomy possibly does have a beneficial effect on the liver disease by reducing the portal hypertension, with consequent increase of the venous circulation and arterial circulation to individual liver lobules.

The decrease in the globulin fraction in the majority of the patients following splenectomy may be explained on the basis of possible improvement of hepatocellular function and also by the removal of one of the major sites of globulin production—the spleen. This decrease in the globulin following splenectomy has not been recorded in the literature previously as far as can be determined.

TABLE V.—SUMMARY OF LATE DEATHS IN GROUP A

	Period of survival post-splenectomy	*Autopsy findings*	*Clinical diagnosis at time of death*	*Pathology of liver biopsy*
Case 9	6 months	None performed	Unknown	Coarsely nodular cirrhosis
Case 13	6 months	None performed	Unknown	Focal portal fibrosis (minimal)
Case 16	12 days	1. Hydroureter and hydronephrosis due to schistosomiasis, ureter, severe 2. Coarsely nodular cirrhosis, and schistosomiasis, liver with extensive venous collateral circulation		
Case 17	Several months	None performed	Unknown	"Pipe stem" portal fibrosis
Case 18	3 days	None performed	Severe anemia	Focal portal fibrosis (minimal)

No significant difference was noted in the liver function tests of those who died following splenectomy and those who recovered.

The effect of splenectomy on portal hypertension. The following observations in this study suggest that the portal hypertension may be reduced by splenectomy in some patients: (a) diminished ascites, (b) decrease in the liver enlargement and tenderness, (c) absence of hematemesis in all cases following splenectomy, (d) improvement in liver function tests and decrease in the globulin fraction.

Although evidence supporting the beneficial effect of splenectomy on portal hypertension has been presented, the effect is believed to be negligible by some workers. Rousselot has shown that if the obstruction of the portal vein is extrahepatic, a definite decrease in the portal hypertension will follow splenectomy. Palmer and Jahnke have suggested that both an extrahepatic and intrahepatic portal venous obstruction may be present in some of the cases of Egyptian splenomegaly. The evidence in this series also suggests this possibility and will be discussed in a subsequent paper (9). Before the effect of splenectomy on portal hypertension in Egyptian splenomegaly is completely understood, direct measurement of the portal venous pressure and direct observation of esophageal varices must be made before and after splenectomy.

Previous studies of splenectomy in Egyptian splenectomy and Banti's syndrome. Abdou and Grace, in a study of 35 patients with Egyptian splenomegaly on whom splenectomy was performed, concluded that removal of the spleen had a definitely beneficial effect in selected cases. Benitez reached a similar conclusion from the study of 20 patients with Banti's syndrome due to schistosomiasis who were in the preascitic stage. The patients in his series were examined from 1 to 18 months after splenectomy. Dias believed that splenectomy was of definite value in this condition by lowering the portal hypertension, removing the hypersplenic factor, and reducing the "vicarious circulation through the esophageal veins, thereby preventing the formation of varices." Stiven performed more than 800 splenectomies on patients with Egyptian splenomegaly. Al-

TABLE VI.—RESULTS OF POSTSPLENECTOMY CLINICAL EXAMINATION IN GROUP B

	No.	*Per cent*
Number of patients with postsplenectomy clinical examination*	67	
Alive, working full time	52	78
Alive, no major complaints, but not working	9	13
Late deaths	6	9

*The interval between splenectomy and the last follow-up examination varied from 3 months to 3 years.

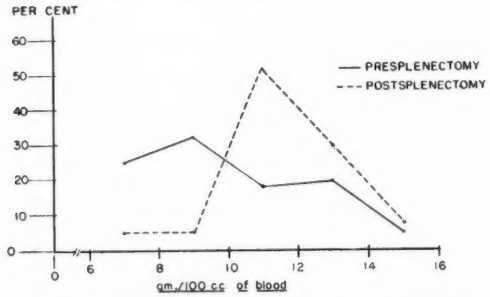

FIG. 5. Distribution of hemoglobin determination before and after splenectomy.

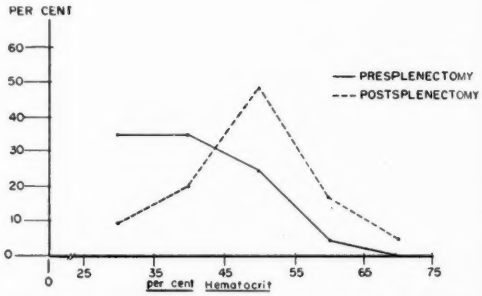

FIG. 6. Distribution of hematocrit determination before and after splenectomy.

though only a small number of these patients received follow-up examinations, it was his distinct impression that the splenectomy was the treatment of choice. The consensus in Egypt at present is that splenectomy should be performed in cases in which there is no evidence of ascites or severe liver damage, in those with signs of hypersplenism and in those in which marked splenomegaly is a mechanical impediment to the physical activity of the patients.

The close similarity clinically between Banti's syndrome and splenomegaly associated with schistosomiasis has been pointed out by Rousselot. In a study of 11 patients with schistosomal splenomegaly, he showed that splenectomy produced consistently excellent results. There was no operative mortality and only 1 patient had died (30 months after splenectomy). The remainder were in excellent health from 2 to 4 years following splenectomy.

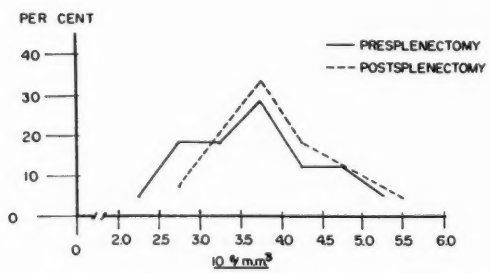

FIG. 7. Distribution of erythrocyte counts before and after splenectomy.

Howells compared 51 patients with Banti's syndrome on whom splenectomy was performed with 43 similar patients on whom the operation was not done. He was unable to demonstrate any difference between the two groups in regard to life expectancy, prevention of the progress of the liver disease, anemia, or the occurrence of hematemesis. Pemberton and Kiernan in a similar study, concluded that splenectomy for portal hypertension should be reserved for young patients with no evidence of impairment of liver function.

Collier and associates, in a study of 27 patients with Banti's syndrome, concluded that splenectomy is probably the treatment of choice for many patients. Follow-up studies in this series showed a 10 year or longer survival rate for 22 per cent of the patients and a 5 year survival for 40 per cent.

Durham has stated that splenectomy in Banti's syndrome probably brings about the following results: (1) decreases portal venous pressure; (2) improves liver function; (3) reduces incidence of hematemesis; (4) corrects thrombocytopenia; (5) does not accelerate the existing cirrhosis.

Portacaval shunts in congestive splenomegaly. The results of portacaval shunts in portal hypertension due to causes other than schistosomiasis have been very encouraging. Childs has performed portacaval shunts in 2 patients with portal hypertension, splenomegaly, and cirrhosis of the liver asso-

ciated with schistosomiasis. Both patients had severe hematemesis prior to the operation. The portacaval shunt reduced the portal pressure significantly in each case, and there had been no postoperative recurrence of the hematemesis after durations of 3 months and 12 months. Palmer and Jahnke have performed the portacaval shunt operation on 2 patients with splenomegaly associated with schistosomiasis with good results. Radiologic evidence of esophageal varices disappeared after the operation. Sayegh has recently utilized the portacaval shunt procedure with good results in 3 patients with Egyptian splenomegaly who had recurrent hematemesis.

Rousselot has recommended a combined (one stage) splenectomy and portacaval shunt as the surgical procedure of choice in congestive splenomegaly. There has been no published report of the employment of this procedure in Egyptian splenomegaly, but, on the basis of its efficacy in other forms of congestive splenomegaly, it would, no doubt, be more beneficial in this condition than splenectomy alone.

Contraindication to splenectomy in Egyptian splenomegaly. We believe that there are contraindications to splenectomy in Egyptian splenomegaly. These are: (1) severe anemia, (2) moderate to marked ascites, and (3) severe renal insufficiency. If anemia alone was present, the patient received whole blood transfusions and ferrous sulfate by mouth. If the red blood cell count could be elevated to above 3 million per cubic millimeter and hemoglobin to 10 grams, the patient was considered to be a reasonably good operative risk and splenectomy was performed. The patients rejected for splenectomy because of these contraindications were few.

Comment. The hospital mortality (7 per cent) in groups A and B of the splenectomized patients at the American Mission Hospital from 1947 through 1953 compares favorably with the operative mortality of patients treated by splenectomy for Banti's syndrome at several institutions in the

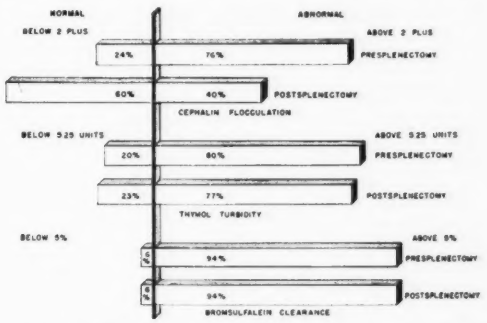

FIG. 8. Three of the liver function tests before and after splenectomy, per cent of normal and abnormal determinations.

United States. The incidence of late deaths (6 per cent) in this series was regarded as low when the poor physical status of the Egyptian fellah and his unfavorable environment are considered. It is our conclusion that splenectomy as a treatment of Egyptian splenomegaly has been neglected and should be used more frequently, even in patients who have definite clinical and laboratory signs of liver disease, portal hypertension, and anemia. As has been shown in this study, the mortality is low when the operation is performed by an experienced surgeon aided by transfusion of whole blood and good anesthesia. The best result that can be hoped for in these patients is to return as many as possible to a physical status at which they are capable of performing the arduous work of agricultural laborers. This goal has been achieved in these patients by means of splenectomy.

SUMMARY AND CONCLUSIONS

1. The clinical results of splenectomy in 135 patients with Egyptian splenomegaly (chronic congestive splenomegaly) have been described. One hundred (74 per cent) of these incapacitated Egyptian fellahs were returned to full time work as agricultural laborers.

2. Hematologic and liver function studies before and after splenectomy indicated an improvement in the majority of the patients on whom the operation was performed.

3. On the basis of the low hospital mortality rate (7 per cent), the late mortality rate (6 per cent), and the definite improvement in the clinical and physiologic status, it is recommended that splenectomy be used more frequently as a treatment of Egyptian splenomegaly, even in patients who have signs of liver disease, portal hypertension, and anemia.

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STRUCTURAL REPRESENTATIONS OF TUMOR-HOST RELATIONSHIPS IN GASTRIC CARCINOMA

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IN 1953 WE REPORTED that the presence of marked sinus histiocytic reactions in the axillary lymph nodes of breast cancer patients was associated with prolonged postoperative survivals. In addition, it was noted that the occurrence of lymphoid infiltration in the primary tumor was also a favorable prognostic sign (1). Similar results were obtained in a later study of survival of patients with gastric carcinoma (2). These structural features were therefore interpreted as representative of tumor antagonistic factors in the host.

In order to explore more adequately the phenomenon of tumor-host interactions we extended our studies of the relationship between survival and the structural features of breast cancer to include the nuclear structure as well as the degree of lymphoid infiltration in the primary tumor and the sinus histiocytic reactivity of the axillary lymph nodes (3, 5). It was found that postoperative survival varied as a function of the nuclear differentiation, lymphoid infiltration of the primary tumor, and the sinus histiocytic reactions of the regional lymph nodes. It was thus possible to utilize these three parameters to create a combined grading system which showed a linear relationship with survival.

In order to determine whether such a combined system of grading had a more general applicability, we undertook a similar study of the survival of patients with gastric carcinoma. The present data confirm the existence of tumor-host interactions in gastric carcinoma. In addition, it would appear that the relationship between the proposed grading system and the survival of gastric cancer patients is essentially identical to the relationship obtained in regard to the survival of breast cancer patients. Our findings lead to the conclusion that the structural features under investigation are of greater prognostic significance than the presence or absence of regional metastases, age of the patient, preoperative delay, or even the site of origin of the tumor (breast or stomach).

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MATERIALS AND METHODS

In the present study, an evaluation was made of the degree of nuclear differentiation and lymphoid infiltration of the primary tumor and the degree of sinus histiocytosis of the regional lymph nodes from patients with gastric cancer followed to death or for a minimum of 5 years postoperatively. Measurements were made of one or more of these parameters in 75 patients known to have survived a minimum of 5 years postoperatively, and in 94 patients known to have died of the disease within 2 years after operation.

The criteria for the evaluation of the nuclear structure, lymphoid infiltration, and sinus histiocytosis have been presented in detail in previous publications (2, 3, 5). The essential features of the grading system employed were as follows:

Nuclear structure (N grade). The nuclear structures were graded from 0 to 4 according to the degree of nuclear differentiation. Large nuclei exhibiting marked chromatin clumping, anisonucleosis, prominent nucleoli, and mitotic figures were evaluated as N grade 0. In contrast, nuclei characterized by small size, marked similarity to one an-

TABLE I.—PER CENT INCIDENCE OF NUCLEAR GRADE IN RELATION TO SURVIVAL

Group	No. of cases	Incidence, per cent Nuclear grade 0	1	2	3	4
⩽2 yrs.	48	17	56	25	2	—
⩾5 yrs.	49	2	49	41	8	—

TABLE III —PER CENT INCIDENCE OF SINUS HISTIOCYTOSIS IN RELATION TO SURVIVAL

Group	No. of cases	Incidence, per cent Sinus histiocytosis 0	1	2	3	4
⩽2 yrs.	82	74	20	5	1	—
⩾5 yrs.	64	67	6	16	9	2

other, delicate chromatin, and inconspicuous or absent nucleoli were judged to be N grade 4. Intermediate degrees of such change were assigned intermediate values in accord with their relation to the extremes of the scale. It should be noted that the significance of the numerical grading used here is opposite to the usual classical histologic grading used by Broders.

Lymphoid infiltration (LI grade). The degree of lymphoid infiltration in the primary tumor was evaluated on an increasing scale from 0 to 4. The latter value was applied to cases showing massive infiltrations of the lymphocytes throughout the tumor with an intimate intermingling of the tumor cells and lymphocytes. This reaction is distinct from inflammatory reactions which are characterized by pleomorphic cellular infiltrate, fibroblastic proliferation, and necrosis.

Sinus histiocytosis of regional lymph nodes (SH grade). The structure of the uninvolved lymph nodes or uninvolved portions of partially involved nodes was evaluated from 0 to 4 in relation to the degree of proliferations of sinus histiocytes. It should also be noted that in those cases in which all the nodes were completely involved by metastatic tumor cells the sinus histiocytic reactivity was graded as 0.

RESULTS

Nuclear grade. In Table I we have listed the incidence of the N grades as found in the long and short term survivors, that is, ⩾5 years and ⩽2 years postoperatively respectively. It will be noted that there was a greater incidence of N grades ⩾2 in the long survival group (49 per cent) than in the short survival group (27 per cent). Conversely, the incidence of N grade 0 was greater in the short survival group (17 per cent) than in the long survival group (2 per cent). The difference in incidence of the various N grades between the two series would appear to be significant as judged by the chi square method of testing ($P<0.01$).

Lymphoid infiltration. In Table II we have indicated the relative frequency of the various LI grades as found in the long and short survival groups. It is evident that there was a decided difference in the frequency with which LI grades ⩾2 were encountered in these two groups of cases. Among the short term survivors such a degree of lymphoid infiltration was noted in only 3 per cent of the cases in contrast with a frequency of 72 per cent in the long survival group. The probability that such differences would be encountered by chance is much less than 1 in 100.

Sinus histiocytosis. As will be noted in Table III SH grades ⩾2 were encountered in 27 per cent of cases comprising the long survival group. On the other hand, the incidence of such lymph node features among the short survivors was only 6 per cent. The observed differences would be expected by chance less than once in a hundred times.

Combined grade. In order to evaluate the significance of the interaction of the grades of the three parameters we have combined

TABLE II.—PER CENT INCIDENCE OF LYMPHOID INFILTRATION IN RELATION TO SURVIVAL

Group	No. of cases	Incidence, per cent Lymphoid infiltration 0	1	2	3	4
⩽2 yrs.	94	85	12	3	—	—
⩾5 yrs.	75	9	19	32	23	17

TABLE IV.—PER CENT INCIDENCE OF COMBINED GRADE IN RELATION TO SURVIVAL

Group	No. of cases	Incidence, per cent Combined grade <2	2	2-2	3+1	⩾5
⩽2 yrs.	33	58	36	3	3	—
⩾5 yrs.	43	2	21	9	23	44

the various grades in an additive fashion. The results of similar procedures as applied to breast carcinoma have been reported previously (3, 5). In the present computations any grade of 0 to 1 was counted as 0. Thus we had the following groups of combined grades (CG): <2, 2, 2–2, 3+4, and ⩾5. Note that we have distinguished between those cases in which any one of the parameters was graded as 3 or 4 while the other measurements were <2, and those cases having two values equal to 2 with the third value <2.

Table IV depicts the relative frequency of the various CG values as found in the long and short survival groups. It will be noted that 58 per cent of the short term survival cases had CG values <2 in contrast to an incidence of only 2 per cent in the long term survivors. Conversely 44 per cent of the long term survivors had CG values ⩾5 while none of the 33 short term survivors had such a combined grade. As judged by the chi square method the probability that the differences in incidence of the various CG values between the two series might be due to chance variation is much less than 1 in 100.

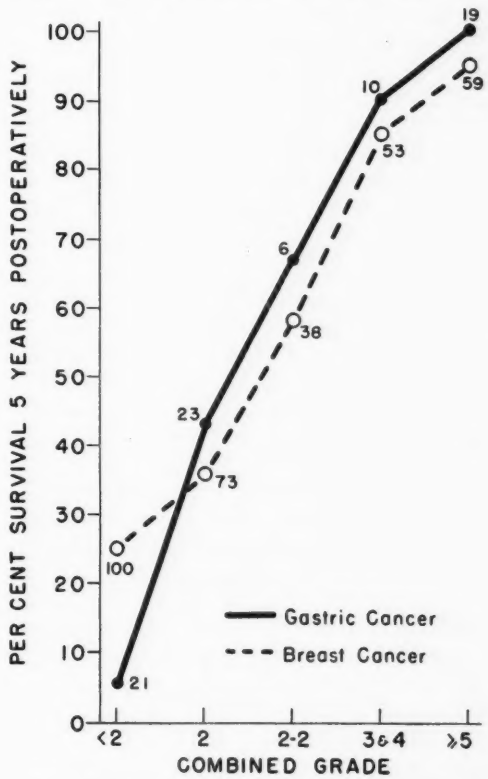

FIG. 1. Relationship between per cent of 5 year survival and combined grade in patients with gastric and mammary cancer. The values at each point indicate the number of cases.

COMMENTS

This study confirms our previous impression that gastric cancer patients having prolonged survivals are characterized by an increased incidence of lymphoid infiltration in the primary tumor or sinus histiocytic changes in the regional lymph nodes (2). It also demonstrates that there is a greater incidence of nuclear differentiation in the long survival group as compared to patients dying of the disease within 2 years.

That these various prognostic features may operate in an additive fashion is suggested by the data of Table IV. This phenomenon is even more clearly demonstrated if we combine the two series of cases and plot the incidence of 5 year survivals in relation to the combined grades. Figure 1 depicts the result of such computations. It will be seen that there is a linear progression of the per cent 5 year survival from 5 per cent (with combined grade less than 2) up to 100 per cent (with a combined grade equal to and greater than 5). It is particularly pertinent to note that this survival curve is almost identical to the analogous relationship which was found in our previous study of the survival of breast carcinoma patients in regard to combined grading.

It should also be mentioned that the presence or absence of lymph node metastases was not found to be a critical factor in determining survival. Thus, lymph node metastases were found in more than 40 per cent of the 5 year survivors, while in 30 per cent of the patients dying within 2 years postoperatively no lymph node metastases were found. Furthermore, it should be emphasized that a

5 year survival is not tantamount to a cure in gastric carcinoma since at least 9 of the 75 patients were known to have died of the disease more than 5 years after operation.

These various data are consistent with the hypothesis that survival in gastric carcinoma is critically related to tumor-host relationships which are depicted in the structural features of the primary tumor and the regional lymph nodes. In our previous studies, we presented data which documented the association between superior survival in mammary carcinoma and certain structural features representing host antagonism. The present study of gastric carcinoma has more than strengthened and confirmed our original impressions in regard to the significance of tumor-host interrelationships in determining the natural history of cancer.

Since mammary gland carcinoma is considered by many current authors to be a curable cancer it was particularly important to determine whether or not similar factors were operable in gastric carcinomas which as a group are so rapidly lethal. The finding that the same biologic factors are associated with superior survival in gastric cancer as in mammary cancer must perforce emphasize that the intrinsic tumor-host relationships are of greater significance in determining survival than is the modality of therapy or the skill of the therapist.

In this connection it is pertinent to note that Macdonald and Kotin came to very similar conclusions which they epitomized under the term, biologic predeterminism (9). They emphasized that early diagnosis does not improve the results of treatment. Their data indicate that under the most ideal circumstances less than 20 per cent of all gastric carcinomas are surgically curable. The limitations of superradical surgery in this field are illustrated in the findings of Harvey and associates in their study of the survival of gastric cancer patients operated upon at the Presbyterian Hospital. They stated, "Curiously enough, there is no statistical evidence that it was important to keep the plane of excision well wide of the growth in the stomach wall. In three of the sixty survivors, the tumor was thought to have been cut through. These patients all lived more than ten years without evidence of recurrence. In an additional eighteen patients, the plane of excision went less than 2 cm. from the tumor in the stomach or the duodenum. In only two thirds of the survivors could it be said that an excision well wide of the growth (i.e. 2.5 cm. or more) had been done. One cannot commend planes of excision that run close to tumors, but these facts support the conception that total gastrectomies for all gastric tumors are unnecessary."

Such findings would be irrational according to the classical concepts of cancer which view malignant neoplastic disease as an expression of an autonomous primary lesion that undergoes progressive dissemination in a linear relationship with time. Based on such a concept any hope of improvement in survival statistics must be limited to a plea for "early diagnosis" by which is usually implied a small tumor. The limitations of such a program for significantly decreasing the cancer death rate has been commented upon recently by Macdonald and McKinnon as well as ourselves (4). While it is undeniable that a small cancer may in some instances actually be an early cancer in the biologic sense, it is also a reality that all too frequently small primary lesions have already disseminated widely. In short, the general assumption that all dwarf-sized cancers must be biologically young is no more valid than the assumption that all human dwarfs must be young because they are small.

There appears to be little doubt that the classical concept of cancer is far too naive and inadequate to encompass the observed behavior of most types of cancer. It leads to the unusual situation of assuming biologic phenomena to be paradoxical, incomprehensible, and associated with more exceptions than rules. In contrast, the concept of tumor-host interactions presents an internally consistent thesis that is in accord with and capable of predicting observed behavior (6). The

fact that even in its present, admittedly crude, form it is capable of reducing such apparently different cancer types as breast and gastric carcinomas to a common denominator is strong indication of the reality of the concept and the applicability of the structural representation presented. The classical concept of cancer would appear to be analogous to the proverbial tired horse. It would seem more reasonable to replace the horse than to get a bigger whip.

SUMMARY

A study was made of certain structural features of gastric cancers and their regional lymph nodes in relation to postoperative survival. The features evaluated were: nuclear differentiation and lymphoid infiltration of the primary tumor, sinus histiocytosis of the regional lymph nodes and combinations of these three parameters. It was found that patients with long postoperative survivals were characterized by the presence of a high grading of one or more of the three parameters. A combined grading system was constructed which yielded a linear correlation with survival. The findings were discussed in terms of tumor-host relationships as a critical phenomenon in determining the survival of cancer patients.

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LUMBOSACRAL FUSION RESULTS WITH EARLY AMBULATION

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PATIENTS UNDERGOING FUSION of the lumbosacral spine for mechanical or structural defects at the New York Orthopaedic Hospital since 1947 have been ambulated during the second to third week following operation. The results in the first group of patients, 106 consecutive cases, have been evaluated and are presented in this report. This group includes fusions for mechanical instability, with or without disc excision and spondylolisthesis. Prior to operation, all of the patients were treated with conservative measures in a low back clinic. The operations were performed by members of the house staff, under the supervision of surgeons of the attending staff. Patients with a diagnosis of a herniated nucleus pulposis were operated upon by a neurosurgical-orthopedic team. A spinal support, corset, or low back brace was applied at the time of ambulation.

Age statistics revealed a variation of from 16 to 60 years; 70 per cent were in the 30 to 50 year age group. Female patients outnumbered males by a ratio of 2 to 1.

In the series, there were 69 fusions from the fifth lumbar vertebra to the sacrum, 35 fusions from the fourth lumbar vertebra to the sacrum, and 2 fusions from the fourth to the fifth lumbar vertebra. The Hibbs fusion method was the basic technique employed in all of the cases in this series. In 20 cases the technique was modified with the use of screws across the articular facets, and in 15 cases an H graft of iliac bone was wedged between the spinous processes after preparation of the fusion bed of bone chips. The fusion mass was re-enforced with autogenous or bank bone in all but 4 of the operations extending from the fourth lumbar vertebra to the sacrum. Twenty-four of the fifth lumbar to sacrum fusions and 1 of the fourth to fifth lumbar procedures had extra bone added at the time of operation. Of a total of 56 operations in which extra bone was used, autogenous bone from the ilium was the source in 49 and bank bone in 7.

Fusion results (Table III). The patients in this series were followed in a special clinic. The same surgeons performed the postoperative interval examinations and were responsible for the final clinical and roentgenographic evaluation 1 year postoperatively. In addition to the usual lumbosacral roentgenograms, lateral views of the fusion area were taken with the spine in forced flexion and extension.

The number of operations for spondylolisthesis is too small to be of statistical significance. Fusion failure in 2 of the 6 operations indicates, however, a higher incidence of pseudarthrosis in spondylolisthesis than in lumbosacral fusions for other types of defects. Of the 2 fusions from the fourth to fifth lumbar vertebra, 1 resulted in a pseudarthrosis.

Clinical results (Table IV). The clinical results 1 year after operation were classified according to the residual symptoms, if present, the clinical findings, and the work capacity of the individual. If the patient had only minor or no complaints, had no significant clinical findings, and had resumed his usual occupation without restrictions, the result was considered good. If specific duty limitations were necessary because of pain, the result was classified as fair. A poor result was recorded for no improvement.

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TABLE I.—INDICATIONS FOR FUSION

	No. of cases	*Per cent*
Herniated nucleus pulposis—unstable lumbosacral spine	76	71
Unstable lumbosacral spine	24	23
Spondylolisthesis	6	6

TABLE II.—TECHNIQUE OF FUSION

Area of fusion	*Hibbs*	*H graft*	*Screw fixation*
L5-S1	37	7	25
L4-S1	22	8	4
L4-L5	2	1	0
Totals	61	16	29

TABLE III.—FUSION RESULTS

		Pseudarthroses	
Area of fusion	*No. of cases*	*No.*	*Per cent*
L5-S1	69	6	8.7
L4-S1	29	5	16.6
Spondylolisthesis	6	2	
L4-L5	2	1	

TABLE IV.—CLINICAL RESULTS

	Good		*Fair*		*Poor*	
Area of fusion	*No.*	*Per cent*	*No,*	*Per cent*	*No.*	*Per cent*
L5-S1	52	75	10	15	7	10
L4-S1	26	90	—	—	3	1
Spondylolisthesis	3		3		—	—
L4-L5	2		—	—	—	—

Analysis of fusion failures. Pseudarthroses, in this series of cases, were found to occur in patients of an average age of 40 years—about the same as the average age of the entire group. Four patients were under 26 years of age. There were no occupational variations compared to the group as a whole. Six patients were engaged in sedentary or light activity, 1 was a laborer, and 7 were housewives.

Extra bone. Of the 6 failures at the fifth lumbar to sacrum level, autogenous iliac bone was used in 5, and in 1 no extra bone was added. In all but 1 of the fourth lumbar to sacrum pseudarthroses, extra bone was added to the fusion—autogenous iliac bone in 4 and bank bone in 2. An H graft of autogenous iliac bone was used in the fusion from the fourth to fifth lumbar vertebra which failed to become solid.

Operative technique. In this series there were fusion failures with each of the 3 operative methods employed, the Hibbs technique, and the Hibbs modified with H graft, or screws. The fusion results were comparable with the exception of the few cases in which screw fixation was used at both the fourth to fifth lumbar and the fifth lumbar to sacrum joints. In 3 of the 4 cases, 1 a spondylolisthesis, in which this technique was used a pseudarthrosis developed.

Pseudarthrosis and symptoms. Of the 14 patients in whom solid fusions failed to develop, 6 or 43 per cent had no significant symptoms.

DISCUSSION

Few statistical reports on results of lumbosacral fusion with early ambulation are available in the literature. In 1948, Cleveland, Bosworth, and Thompson published their results in a large series of cases and reported a failure of 3.2 per cent of the fusions of fifth lumbar to sacrum and of 17.4 per cent when the fourth lumbar vertebra was added. These authors made the statement that "postoperative care in most cases was 2½ to 3 weeks of bed rest, thereafter, a lumbosacral belt re-enforced with light steel."

King reported a series of 55 lumbosacral fusions with internal screw fixation. The patients were ambulated 3 weeks postoperatively, some with braces. There was a pseudarthrosis rate of 10 per cent in this group of cases. King did not report separate figures for fusions of fifth lumbar to sacrum and fourth lumbar to sacrum.

Thompson and Ralston, in a study of all spine fusion operations performed at the New York Orthopaedic Hospital from 1936 through 1945, reported a pseudarthrosis rate of 8 per cent of the fusions of the fifth lumbar to sacrum, and of 24 per cent when the fourth lumbar vertebra was included. The patients were kept in bed 6 to 8 weeks postoperatively with plaster or brace immobilization. These authors included in their series a group of 90 patients with internal screw fixation, ambulated 2 to 3 weeks postoperatively without external spinal support. Of 41 fifth lumbar vertebra to sacrum fusions with screws, 12 per cent failed to become solid. With the inclusion of the fourth lumbar vertebra, in 49 cases, the fusion failures increased to 55 per cent.

Since the fusion failures in Thompson and Ralston's cases with screw fixation at the fifth lumbar to sacrum level did not increase significantly with early ambulation, what is the explanation for the marked increase in pseudarthrosis when the same operative technique was applied to a two joint fusion? There is reason to believe that screw fixation of the facets at the fourth to fifth lumbar vertebra level is less secure than at the lumbosacral joint where the sacral processes afford better anchorage for the screws. In placing the screws in the lamina, a certain amount of bone, otherwise available for chips, is utilized, thus lessening the effectiveness of the fusion bed. This may be of more significance in fusions of the fourth lumbar to sacrum because of the higher incidence of failures when the fourth lumbar vertebra is added, regardless of the operative technique.

In the cases included in this report, the percentage of failures of the fusions of fourth lumbar vertebra to sacrum was 16.6 per cent as compared to 24 per cent in Thompson and Ralston's cases with longer periods of postoperative recumbency. This improvement may be due to the almost routine use of extra bone and the infrequent use of screws at the fourth to fifth lumbar vertebra level. There was no indication that early ambulation had an adverse effect on the development of a solid fusion of the lumbosacral spine.

CONCLUSIONS

1. At the New York Orthopaedic Hospital, the results of lumbosacral fusion in patients ambulated 2 to 3 weeks postoperatively compare satisfactorily with the results after longer periods of postoperative recumbency.

2. In this series of 106 cases, the incidence of pseudarthrosis was approximately doubled when the fourth lumbar vertebra was included in the fusion.

3. A larger group of patients must be studied for a significant evaluation of operative methods, of the use of extra bone, and of the merits of autogenous versus bank bone as related to the incidence of pseudarthrosis in lumbosacral fusion.

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CARDIAC ARREST

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NO MORE INTENSE DRAMA in the operating pavilion ever is enacted than that occasioned by the catastrophe of cardiac arrest. Although there have been many published reports of series of cases with attempts at analysis of cause, and even though much basic research has been going on in this field, still, our knowldge of causative factors is so sketchy as to make prevention less effectual than is desired. Anoxia and carbon dioxide accumulation are well recognized as etiologic but there still is an uncomfortable feeling among surgeons that the ever increasing complexity of anesthesia gadgets and the always mounting numbers of powerful adjuvant drugs which may exert as yet unknown synergetic effects may be the initial cause of anoxia.

The increasing interest in cardiac arrest during recent years has resulted in the development of rather standardized management of this catastrophe. Numerous reports indicate a similar survival rate when definitive treatment is promptly instituted. Since solution of this problem can be expected only as the summarization of factors from many reports contribute to our knowledge, it seems advisable to add our experience to the literature. The recognition and treatment of cardiac arrest has been mastered to some degree, but further progress seems possible in the field of prophylaxis. In July 1953, at Brooke Army Hospital it was noted that there had been a considerable increase in the number of cases of cardiac arrest with a discouraging end result. It was the impression that the increase was due to the greater seriousness of the cases being treated surgically and the rapidly increasing cardiac surgery load with its share of poor risk patients. The problem was considered at a general staff meeting where a symposium was held. The several aspects of cardiac arrest were presented by speakers from cardiology, surgery, and anesthesiology services. The effectiveness of staff indoctrination is evidenced by the more frequent recognition of arrest and consequent increased resuscitation and survival rates after 1953, as shown in Table I. The general alertness resulting from staff indoctrination no doubt is an additional factor accounting for the difference in figures of the two periods studied.

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METHOD OF STUDY

Arbitrary differences in the methods of calculation of incidence in published reports rendered it difficult to compare our results with those in the literature. Consequently, incidence was calculated in two ways: the ratio of arrests based on inhalation anesthesia, and the ratio of arrests based on major operations performed (Table II). This latter ratio more nearly compares with the method of calculation used in other reports; 85.7 per cent of the patients studied received general anesthesia.

The 28 cases herein reported occurred at Brooke Army Hospital over a 5 year period, 1950 through 1954, inclusive. All cases were studied in which a diagnosis of cardiac arrest was made.

PRESENTATION OF MATERIAL

Children. Among the 10 children, the ages ranged from 3 weeks to 11 years. There were 2 good risk patients and 8 poor risk patients, 1 of whom was considered hopeless.

TABLE I.—EFFECT OF STAFF INDOCTRINATION ON RESULTS

Period	*No. of cases*	*Resuscitated*		*Survival*	
		No.	*Per cent*	*No.*	*Per cent*
Before staff conference—1950 to Sept. 1953.....	8	2	25	1	12
After staff conference—Sept. 1953 to Jan. 1955.	20	12	60	6	30

Chronic anoxia existed as a factor of the primary disease in 8 patients. Six of this group had congenital heart disease and 2 others had combined contributory factors (physiologic imbalance with intracranial pathology, and physiologic imbalance with marked abdominal distention).

Significant factors contributing to arrest such as anoxia, circulatory deficit, or toxemia existed in 7 patients prior to the induction of anesthesia. In 2 patients contributory factors were manifest during induction. Eight patients received gas-oxygen-ether anesthesia, 1 received avertin-nitrous oxide and oxygen, 1 received local novocain infiltration. Arrest developed during operation in 8 patients and during induction in 1 patient. One patient developed arrest in the postoperative period. This followed respiratory difficulty which existed throughout an intracranial operation. Positive mechanisms which initiated arrest are noted in 8 patients: intracardiac or great vessel manipulation in 4, massive hemorrhage in 1, acute hypoxia due to faulty position of the endotracheal tube in 1, endotracheal aspiration in 1, and position change in 1.

The treatment of arrest in all cases was rhythmic cardiac compression. The defibrillator was used on 1 patient only. One patient survived without sequelae. Arrest occurred in 8 patients, ventricular fibrillation in 2 patients. One patient survived 14 hours. It is of interest that 3 patients were undergoing diagnostic cardiac study and 7 patients were undergoing surgery.

Adults. Eighteen of the patients studied were adults. The age range was from 15 to 68 years. Thirteen of the group were under 50 years. Thirteen were "poor risk" patients; 5 were "good risk" patients. Thirteen patients had chronic anoxia as a significant factor of the primary disease. Of this group 8 were considered "hopeless" cases. The anoxia was attributable to chronic cardiac disease in 4 patients and toxic states in 9 patients.

Chronic anoxia, circulatory deficit, or physiologic imbalance, factors favoring the development of cardiac arrest, existed prior to surgery in 12 patients and were manifested in the operating room in 3 patients. Fourteen patients received gas-oxygen-ether anesthesia, 1 patient received amytal, 1 patient received pentothal-curare-ether, and 1 patient received an epidural block for pain. Arrest developed during operation in 10 patients, during the induction of anesthesia in 4 patients, and postoperatively in 3 patients. One arrest developed during tracheal aspiration in a patient with pulmonary edema.

Possible trigger mechanisms initiating arrest are noted in 14 patients. Sudden hemorrhage during the course of operation initiated arrest in 3 patients. One patient developed arrest on intracardiac manipulation. Tracheal stimulation resulted in arrest in 3 patients. One of these developed ventricular fibrillation during tracheal intubation 7 days after the arrest. This patient survived both catastrophes to die of his disease 36 days later. The combination of moderate blood loss and position change produced arrest in 2 patients. Acute hypoxia resulted in arrest in 4 patients. Amytal injection initiated arrest in 1 patient.

Treatment was carried out on 17 patients 18 times; 1 patient was not treated, 1 patient was treated once for arrest and a second time for ventricular fibrillation. Electrical defibrillation was used on 2 patients, successfully on 1.

The results are summarized in Table V. Nineteen patients exhibited factors favoring cardiac arrest prior to anesthesia, 5 patients developed prodromata during induction of anesthesia, and positive trigger mechanisms were recognizable in 23 patients. Seventy-five per cent of the patients had chronic anoxia states due to disease.

TABLE II.—INCIDENCE OF CARDIAC ARREST

	1950	*1951*	*1952*	*1953*	*1954*	*Total*
Uncorrected incidence of cardiac arrest	1	4	1	7	15	28
Corrected by excluding "hopeless" cases	1	4	1	4	9	19
Inhalation anesthetics given	9,020	10,265	11,310	6,350	3,778	40,723
Ratio of arrest to anesthetics given in 28 cases	1:9020	1:2566	1:11310	1:907	1:251	1:1454
Inhalation plus spinal and local for major operations	15,339	11,645	12,292	11,053	5,704	56,033
Ratio of arrest to total anesthetics in corrected series	1:15339	1:2911	1:12292	1:2762	1:634	1:2949

In Table V, "resuscitated" means that it was possible by rhythmic cardiac compression and other means to re-establish a regular heart beat which would continue unassisted. All other cases are counted as "expired immediately" in the "end result" column. In the resuscitated patients who subsequently expired, the "final" death occurred from 2 to 24 hours after successfully re-starting the heart, and here we presume that myocardial damage from anoxia was the cause of the "second" death. Of the 7 patients who have survived, none has had permanent brain damage and only 1 has had temporary brain damage with later complete recovery. Since in a number of cases there was an irreparable original condition which soon would have been fatal even without cardiac arrest, the results are shown in the series, excluding the "hopeless" cases which represent staff optimism and the "never-say-die" attitude. These figures are interesting in that they show 68.4 per cent of the patients were resuscitated and 42.1 per cent of the group survived.

TREATMENT OF CARDIAC ARREST

There should be no difficulty in establishing the diagnosis and immediate institution of treatment during a thoracic operation. The aorta may be palpated for pulsation during an intraperitoneal operation. Excluding either of these two operative fields it has been our policy to check the femoral pulse because of its accessibility. No time should be wasted on cardiac ausculation. The simultaneous efforts of a co-ordinated team are directed toward establishment of an open controlled airway and exposure of the heart. The left chest is opened through the left fourth or fifth interspace, the hand is inserted into the chest and cardiac compression started. Initially the pericardium is not opened since the institution of circulation is of prime importance. Compression is carried on at a rate of 80 to 100 per minute; if weak contractions are present they are reinforced by compression. The rhythmic inflation of the lungs is synchronized with the compression rate, a ratio of approximately 1 to 4. Weak contraction may be bolstered with 1 to 2 cubic centimeters of adrenalin preparation (1 c.c. of 1:1000 adrenalin in 9 c.c. of saline) given directly into the ventricular chamber. Calcium chloride solution 1 per cent may be given in 5 to 10 cubic centimeter amounts to aid the flabby weak heart. Compression of the aorta during the period of rhythmic cardiac compression is of value in assuring coronary and cerebral blood flow.

Rhythmic cardiac compression is instituted immediately if ventricular fibrillation is found to be the cardiac difficulty. The electrical defibrillator is prepared, and if massage does not produce a normal rhythm the electrodes are put on and electrical current applied. Following this, rhythmic cardiac compression is continued in an effort to establish a sinus rhythm.

To facilitate early treatment, sterile packs containing necessary instruments are always available in operation suites and recovery rooms. Sterile defibrillator electrodes are packed separately but kept with the instrument packs. Such equipment is readily available to take care of those cases occurring outside the operating room.

The aforementioned basic treatment has been used in 25 cases herein reported, 1 case

TABLE III.—CHILDREN

Age	*Patient's disease*	*Anesthesia*	*Prodromata*	*Surgical procedure*	*Time of arrest*	*Time lapse, mins.*	**Treatment, result*
11 mos.	Cyanotic heart disease	GOE	Vascular shunt, chronic anoxia	Potts' operation	Occlusion of pulmonary artery	0	C 0
3 yrs.	Aortic pulmonary window	GOE	Digitalized, vascular shunt, chronic anoxia	Repair	Hemorrhage from tear of window	0	C 0
13 mos. (GR)	Megacolon	GOE	Change of position from recumbent to lithotomy	Resection and pull through	At conclusion of operation	3-5	C 0
8 wks.	Coarctation, i. v. septal defect	N	Digitalized, chronic anoxia, pulse rate: 160, temperature: 100°	Angiocardiogram	Passage of bolus	Fibrillation, 1-2	C 0
2 yrs.	Congenital heart disease with failure	A-N_2O-O	Chronic anoxia	Cardiac catheterization	Intracardiac manipulation of catheter	1	C +
11 yrs. (H)	Chronic heart disease	GOE	Aortic insufficiency, BP 170/0, Chronic anoxia, dec. cardiac res., failure	Hufnagel valve	Cross clamping of aorta	Fibrillation, 0	C, defib. 0
6 mos.	Meningitis with hygroma	GOE	Respiratory diff. during surgery	Craniotomy	Early postop. period	3-4	C 0
3 wks.	Intussusception	GOE	Intestinal obs. 24 hr. extreme abd. distention. Physiologic imbalance	Abd. exploration (planned)	Early induction	1	C 0, 14 hrs.
11 mos.	Congenital harelip	GOE	Cyanotic induction	Repair	On tracheal aspiration during operation	1-3	C, thru abd. 0
11 yrs.	Tetralogy of Fallot	GOE	Chronic anoxia, cyanosis on exertion	Cardiac catheterization	20 hrs. 20 mins. anes., endo. tube poorly placed	2	C 0

(GR), good risk; (H), hopeless case.
GOE, gas-oxygen-ether; N, novocain; A-N_2O-O, avertin-nitrous oxide-oxygen.
*C, cardiac compression; 0, expired; +, survived.

was treated by compression via the abdomen, 1 was treated with stimulants alone, no treatment was utilized in 1 case.

DISCUSSION

The cessation of cardiac action is to be expected and accepted in the elderly patient with an incurable disease of any type. Such an attitude formerly included children afflicted with congenital heart disease. Yet with the ever widening scope of modern surgery more and more patients of both groups are being offered palliative operations. Cardiac arrest occurring in such patients during the course of anesthesia and operation is no less a catastrophe than the arrests that may occur in the good risk patients. Although intensive treatment is always instituted despite the relatively hopeless outlook, as might be expected, the response is usually poor. It is in this group of patients that the planned prevention of cardiac difficulty can effectively lower the mortality rate attributable to cardiac arrest.

The majority of the patients presented in this report fall into a bad risk classification, and review of the pertinent points relating to them indicates that certain common denominators merit specific consideration in the prevention of cardiac arrest in the susceptible individual. The glib labeling of such patients as poor risks is no longer acceptable. Instead, it should be possible to designate accurately certain patients as "cardiac arrest suspects" prior to operation. Such a designation can be made on the basis of the patient's disease and clinical condition if one carefully considers the physiologic alterations which are present as a part of the disease state. Thus it should be evident that casual clinical impressions have no place in the management of such patients.

TABLE IV.—ADULTS

Age, yrs.	*Patient's disease*	*Anesthesia*	*Prodromata*	*Surgical procedure*	*Time of arrest*	*Time lapse, mins.*	**Treatment, result*
49	Luetic heart disease, aortic insuf. nodal block	GOE	BP 160/50, chronic anoxia	Hufnagel valve, cardiac massage	Early induction	1-2	C +
66 (H)	Acute pancreatitis	EB	Chronic electrolyte imbalance, moribund	Block for pain	Change of position fol. block—arrest 15 min. later	2	C 0
29 (H)	50 per cent 3rd degree body burns; 10 per cent 2nd degree	GOE	Chronic electrolyte imbalance, chronic sepsis, chronic anoxia	Skin grafting	Early in course of operation	3-5	C 0, 8 hrs.
33 (H)	HG poisoning	I.V. amytal	Chronic anoxia, severe electrolyte imbalance	Artificial kidney (planned)	On start of amytal injection	3.5	C, O 0
23	35 per cent body burns	GOE	Chronic anoxia, toxemia	Skin graft	Intubation: 1, arrest. 7 days→ 2, fibrillation	1-2 1-2	C, +† C, +
34 (GR)	Granuloma (r.m.l.) lung	GOE	30 min. cynosis in lateral position, bronchospasm	Wedge resection	During closure of chest wall	Responded to correction of endo. tube	+mild cerebral signs
61	Chronic intestinal obstruction	GOE	Marked abd. distention, cyanotic induction, electrolyte imbalance	Exploratory laparotomy	Early induction (withstood subtotal gastrectomy later)	Fibrillation, 1-2	C +
41 (GR)	Carcinoma breast	GOE	Hypoxia in colored female	Simple mastectomy	Early in operation	1 and aortic occl.	C +
55 (GR)	Postradiation sinus tract in neck	GOE		Excision (planned)	Early induction (withstood surgery later)	1-2	C +
44 (H)	Aortic stenosis with failure	GOE	Chronic circulatory deficit, chronic anoxia	Aortic vulvotomy (attempted)	Intracardiac manipulation	Fibrillation, 0	C, defib. 0
66 (H)	Arteriosclerosis, bleeding abd. aneurysm	GOE	Preop. BP 98/60, known hypertension with bleeding, 6 hrs.	Resection and graft (planned)	Exploration of aneurysm—mass hemorrhage		0‡
68 (H)	Carcinoma, left lung	GOE	Decreased pul. function marked inanition	Palliative resection (planned)	Hemorrhage from tear in pulmonary vein	0	C 0
40 (H)	Carcinomatosis	GOE	Extreme inanition	Craniotomy hypophysiectomy	Hemorrhage from ext. cerebral artery	1-2	C 0
42 (GR)	Recurrent disc	GOE	Prone position, mod. blood loss	Laminectomy	On return to recumbent position	5	C 0**
15 (GR)	Arthrosclerosis	GOE	Prone position, mod. blood loss	Laminectomy	On return to recumbent position	7-8	C 0
48	Recurrent thyroglossal duct sinus	P-C-E	Cardiomegaly, 190/100, hypertension, 40 min. cyanosis, diff. intubation	Excision	During postop. bronchoscopy	1-2	Drugs 0
23	Obstructive jaundice	GOE	Hypertensive and hyperactive, 6 hrs.	Choledochojejunostomy	6 hrs. postop.	1-2	C 0, 18 hrs.
19 (H)	Glomerulonephritis	0	Acute pul. edema, cyanosis		Tracheal aspiration		C 0

H, hopeless case; GR, good risk.
GOE, gas-oxygen-ether; EB, epidural block; P-C-E, pentothal-curare-ether.
*C, cardiac compression; 0, expired; +, survived and sequela.
†Two arrest, one fibrillation—survived 26 days; arrest on intubation—7 days later fibrillati on intubation.
‡Not treated because of nonremediable lesion.
**Convulsing death, 8 hrs.

Marked heart disease (either congenital or acquired), marked toxemia and inanition states, cardiac decompensation, chronic cyanosis, toxic states evidenced by a long period of temperature elevation, anemia, respiratory embarrassment either from mas-

sive pulmonary parenchymal changes or from mechanical factors which limit respiratory exchange, and chemical imbalance resulting from the disease state appear repeatedly in the patients studied and thus are considered the prodromata of cardiac arrest. Individually or together these factors serve to create a state of chronic anoxia. Accumulated reports to date—by Sloan and by Stephenson and Stilwell and their associates—have indicted anoxia as the villain in the drama of arrest.

The fact that a patient can adapt his existence to a state of chronic anoxia does not imply that he can also weather the storm of anesthesia and operation. The existence of positive prodromata of arrest in a patient necessitates careful investigation of the physiologic factors which might be producing either marked or subclinical anoxia. Not only is the oxygen content of the blood lowered in such patients but some degree of carbon dioxide retention exists. Preparatory preoperative studies are necessarily more extensive than those usually required for the good risk patient. Competent cardiac evaluation is essential. Such an evaluation will include circulation time, venous pressure, electrocardiogram, and cardiac catheterization when indicated. Laboratory studies must include the usual cell counts and hemoglobin determination. Determination of the oxygen content of the arterial blood is important. The Evans blue study will give a workable knowledge of the patient's circulating volume. Serum sodium, potassium, chloride, and carbon dioxide levels aid in clarification of the patient's status. The efficiency of the renal function must be determined. We have found the Fantus test for urinary excretion of chlorides to be of value, particularly when the laboratory figures of blood levels are inconsistent with the patient's clinical condition. This is especially true in patients who have been on a salt-free diet for a prolonged period.

Once the afore-mentioned studies have been completed necessary supportive measures aimed at bolstering the patient's reserves should be instituted. Certain of the studies may have to be repeated to evaluate the patient's response to corrective measures prior to operation. Only by the utilization of such a plan can the patient come to surgery at the optimal time. *The value of unhurried preparation far exceeds the most heroic emergency efforts.* This careful preparation is not limited to one field of surgery. Though cardiac arrest is somewhat more frequent in thoracic and cardiovascular operations, it may occur during neurosurgical, abdominal, and orthopedic operations, and during the course of diagnostic cardiovascular studies.

Reports which have dealt with cardiac arrest have exhibited a primary interest in treatment, yet some of these reports have listed factors which initiated arrest with the greatest frequency. Any consideration of trigger mechanisms must of necessity deal with two types. Acute hypoxia may act either directly on the chronically anoxic myocardium or it may produce a central cerebral depressant effect which results in a vagal arrest of the heart. Otherwise, the trigger mechanisms for the most part seem to fit readily into the vagal reflex pattern. The status of the vagovagal reflex is not well understood and undergoes repeated investigation. Thus far its part in cardiac arrest has not been convincingly discredited. Sloan has demonstrated experimentally that vagal reflexes will produce cardiac arrest in normal animals in severe hypoxic states. It is generally accepted that anoxia per se sensitizes the heart for response to stimuli applied to areas of vagal innervation. Sites of vagal innervation are subject to stimulation by the anesthetist as he works within the trachea, by the thoracic surgeon dealing with either pulmonary or vascular disease, and by the abdominal surgeon as he deals with problems within the upper abdomen. Stimuli applied over the carotid sinus may initiate cardiac difficulty. Regardless of nerve pathways concerned, the following trigger mechanisms appear frequently: tracheal stimulation, airway obstruction, intra-

TABLE V.—SUMMARY OF RESULTS

	No. of cases	*Resuscitated*	*End result*	*Remarks*
Children	10	2	1 recovered, 1 expired in 24 hours, 8 expired immediately	
Adults	18	12	6 recovered, 2 survived 8 hrs., 1 survived 18 hrs., 6 expired immediately	1 had temporary brain damage with complete recovery, 1 died with generalized convulsions, 2 underwent further surgery later, 1 survived a second arrest
Total	28	14 (50 per cent)	7 complete recovery (25 per cent)	
Corrected by excluding hopeless cases	19	13 (68.4 per cent)	8 survived (42.1 per cent)	

cardiac or great vessel manipulation, traction on pulmonary hilar structures, sudden hemorrhage, mild or moderate, marked change of the anesthetized patient's position. Anesthetist and surgeon must be constantly alert regarding the recognized trigger mechanisms and avoid or minimize these when possible.

The cardiac arrest suspect poses additional problems for the anesthetist and cannot be safely handled in a routine manner. Here again, the chronic anoxic state necessitates individualized attention; the realization that such a state may exist without cyanosis is of primary importance. In many patients cyanosis does not develop until the oxygen tension of the blood has reached a critical level. Those experienced with combat casualties are aware that cyanosis may not develop in the severely shocked patient until blood replacement is well under way. The recognition of cyanosis in the "suspect" patient denotes the existence of a catastrophic state resulting from previously unrecognized anoxia. The variable ability of several observers to recognize cyanosis renders this color change valueless as an early indicator of anoxia; rather it might be considered a terminal sign.

The response to narcotics is altered in the suspect patient and only minimal doses are acceptable; the drug of choice should be that with the least depressive effect. One author has specified the routine preoperative use of atropine in the good risk patient. Such a recommendation must be qualified for the suspect group as the vagal blocking effects of this drug must be weighed against the hazards which may result from thickened bronchial secretions which will limit the respiratory exchange. Curare-like drugs used freely in the good risk patients are more dangerous in the cardiac arrest suspects who usually require maximal effort of the respiratory muscles to maintain life.

The dangers of anesthesia induction are accentuated in suspect patients. This observation is more readily appreciated when it is recalled that large doses of any of the anesthetic gases administered to an animal heart-lung preparation produce an immediate dilatation of the heart. Oxygen in 100 per cent concentration is not without danger, as it may eliminate the fine cerebral balance essential for vital reflexes. Endotracheal tubes must be positioned rapidly and accurately with a minimum of trauma in order to prevent either a brief hypoxic episode or prolonged vagal stimulation. Rapid induction techniques have no place in the conduct of anesthesia for these patients. In many instances a properly conducted induction period may require more time than the operative procedure. The choice of anesthetic agent should be dependent upon the experience of the anesthetist. A multiplicity of drugs is not advisable. An individualized nitrous oxide, oxygen, ether combination has seemed safest in our experience.

Careful observation of the accepted physical signs by the anesthetist is absolutely essential. Prompt corrective measures must be

instituted upon the recognition of tachypnea, hyperpnea, early dilatation of the pupils, or variation in pulse or blood pressure. Satisfactory oximeters will probably be available for general use in the future. Currently, these instruments are useful in detecting changes from base-line oxygen determinations. The cardiotachyscope is generally used in patients undergoing cardiac surgery. It offers additional safety when a competent individual is present to monitor the electrocardiographic pattern. Leads 1, 2, and 3 are satisfactory for the detection of gross changes which might herald increasing oxygen deficit. Following a base-line check of these three leads, number 2 has been used to follow the patient throughout the operation. The following signs are considered significant of difficulty: change in the pacemaker site, depression of the *ST* segment, inversion of the *T* wave, widening of the *QRS* interval indicating delayed conduction, ventricular rhythm which might lead to tachycardia or ventricular fibrillation. The use of the cardiotachyscope is indicated in all types of surgery performed on the "cardiac arrest suspects." Regardless of the additional gadgets which may be developed, careful continuous observation of the physical signs will be the secret of safe anesthesia in these patients. Induction difficulties not readily corrected should make postponement of the operation mandatory.

The conduct of operation on a "suspect" patient requires careful attention to technical details. The minor risks incident to most major surgery assume major significance in these patients. Pre-existent anoxia can be as detrimental to tissues as the stagnant anoxia of shock. Unhurried gentleness is essential. The thoracic surgeon must be constantly alert to detect unusual motion of the diaphragm or mediastinum and cognizant of the volume of blood loss and color of the blood. Occasional observation of the aortic pulsations or heart action is of value in detecting impending arrest. The tone of the abdominal muscles is a valuable sign for the surgeon working within the abdomen, as rapidly changing tone may herald cardiac difficulty. The patient's hypersusceptibility to vagal irritation makes it imperative that, when possible, traction on the hilar structures and stomach be minimized. Intracardiac and great vessel procedures should be planned and conducted in such a manner that the patient can be given periods for supportive stabilization as frequently as indicated during the operation. "Cardiac arrest suspect" patients are poor subjects for technical teaching, as their precarious state precludes any unnecessary prolongation of operating time. The appearance of one or a combination of prodromal signs of impending cardiac arrest necessitates the immediate cessation of operative procedures and institution of resuscitative measures.

Emergency operations will occasionally be necessary on "suspect" patients and in this group an increased frequency of arrest will continue to be evident, since rapid emergency preparation offers only minimal reserve support to such patients.

SUMMARY

The accomplishments of an educational program regarding cardiac arrest are evidenced by an increased resuscitation rate and ultimate survival rate. Twenty-eight cases of cardiac arrest at Brooke Army Hospital over a 5 year period through December 1954 are presented. All cases in which the diagnosis was made are included. The corrected series of 19 patients derived by deleting hopeless cases shows an arrest ratio of 1 to 2,143 to inhalation anesthetics or of 1 to 2,949 to major operations performed.

Seventy-five per cent of the patients were of the so called bad risk type. The case material has been analyzed by age group, with particular attention to detrimental physiologic factors existing as a part of the patient's disease. Cardiac diseases and toxic states tend to render such patients cardiac arrest suspects. Analysis reveals anoxia to be the common denominator. Positive prodromata of arrest were present in 67.8 per cent of the patients studied and positive

trigger mechanisms were evident in 78.5 per cent. The generally accepted treatment used in these patients has been briefly reviewed.

There was a 50 per cent incidence of successful resuscitation among the 28 cases. It is of interest that an appreciable death rate occurred 2 to 24 hours after resuscitation, resulting in a survival rate of 25 per cent. Thus, even after self-sustaining rhythm was reestablished, myocardial reserve in 25 per cent of the patients was insufficient to maintain cardiac action.

Definitive prophylaxis of cardiac arrest, in the suspect type patient, is dependent upon accurate physiologic evaluation of the patient's disease, preoperative fortification of the patient's reserves, and careful individualized conduct of anesthesia and operation.

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CESAREAN SECTION

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BY THE END OF 1954, a total of 158,498 deliveries and 5,407 cesarean sections had been performed at the Margaret Hague Maternity Hospital. These have embraced all types of techniques and nearly all of the many indications whose validity has been recognized. This number would seem to be a sufficiently large experience, variously analyzed from time to time, on which to base conclusions.

INDICATIONS

1. In the pre-Sanger era, cesarean section was indicated in the presence of fetopelvic disproportion, only for impossible vaginal deliveries, living or dead. With the introduction of the Sanger operation, it was indicated also for impossible vaginal deliveries of living children; later for relative degrees of disproportion making it difficult for vaginal delivery of living children.

2. Labor inadequacy of the expulsive forces, without necessarily demonstrably serious degrees of fetopelvic disproportion, constitutes an indication almost equally important. In a little more than half the cases, labor difficulty appears to depend most importantly on this functional factor, and it complicates another group in which actual disproportion does exist as the most important factor. In some situations, in which all other conditions are equal, the possibility of vaginal delivery depends solely on the functional activity of the uterus.

A few cases of failure of labor due to faulty uterine function are resolved by stimulating that function by very minute doses of pitocin administered in very dilute solution by the intravenous route. This method must be very cautiously employed under strictest, constant supervision. It is by no means always successful.

In regard to relative disproportion, there are a number of recognized authorities who believe that it is within the competence of any qualified obstetrician so accurately to estimate the size and configuration of the individual pelvis and the size of the baby which shall pass through it that the selection of vaginal delivery or cesarean section can be predetermined. This ability permits the employment of the operation under absolutely ideal conditions and the surgeon is left completely free as to his choice of operative technique. In the practice of these individuals, therefore, labor itself is not employed as the touchstone of determination as to whether cesarean section shall or shall not be employed. In our experience, we have not been able to attain to such omniscience. There is a group of cases which remains indeterminate as to the necessity for abdominal delivery until after observation during actual labor performance has demonstrated the influence of the many intangible factors concerned in labor besides the merely dimensional and conformational characteristics of the mother's bony pelvis and of her fetus. While this group of cases is relatively small in proportion to the whole material, being well within 2 per cent thereof, it comprises a large proportion of the patients who are subjected to cesarean section.

In some of this group, prior estimate of the pelvis will determine the management within the limits of a labor test so short as not to alter seriously the conditions under which the operation must be undertaken. But there are other cases which are so equivocal in their potentialities, or in which judgment may be in error, that before recourse to cesarean section a longer test of labor is required. Thus, the conditions

under which it is at last resorted to may be more or less seriously compromised. This group constitutes the highly important one to which special technical modification of the operation must be applied; otherwise, the patient may be deprived of her chance of escaping cesarean section or, on the other hand, may be subjected to inordinate risk if accorded its benefits. Such observation of a patient's behavior in actual labor is, of course, the more necessary if the validity of the functional indication, as expressed previously, is admitted.

3. Another group of mechanical indications embraces presentation of the fetus. Malpresentation does not per se constitute such indication. But individualization of cases validly indicates the operation in some instances. In breech presentation the concurrent finding of cephalopelvic disproportion of even slight degree may represent high hazard to the fetus and justify the operation. Some cases of transverse presentation indicate cesarean section, for it is increasingly recognized that podalic version, formerly almost wholly relied upon in this situation, is per se one of the most dangerous of all obstetric procedures. Section is therefore increasingly substituted for it in the management of this pathologic finding. In relation to all these situations, corollary consideration of the mother's age, parity, and obstetric history may weight the decision as to the advisability of section. Cesarean section in prolapse of the cord in situations not permitting expeditious vaginal delivery will occasionally save a fetus.

4. A large number of miscellaneous conditions constituting mechanical interference with vaginal delivery may indicate section. Among them are stenoses of the lower birth tract, congenital or acquired tumors of the uterus or adnexa, malpositions of the uterus, old repairs of prior obstetric damage to the bladder or birth tract, old injuries to the bony pelvis, and prior cesarean section.

The validity of the last indication is to some extent debatable. "Once a cesarean section, always a cesarean" is adhered to by many obstetricians either on the basis of reasoned conviction or of unfortunate experience. They say that cesarean section scars do rupture, that if they do a very grave situation for the mother exists, that some of these women die, and that nearly all the babies do. Therefore, they insist that one has no right to gamble with the lives of mothers and babies and that the obstetrician has the responsibility of protecting both by the relatively innocuous election of cesarean section.

Those who do not subscribe to the validity of the axiomatic statement quoted point out that vaginal delivery, on the basis of broad statistics, is safer for the mother than section by about 2 to 1; that vaginal delivery does not limit the mother's fecundity; that a uterus once wounded is a "crippled" uterus in the phrase of those who do not trust such wounds; that to wound it over and over again is as much an insult as to do it the first time; that this fact necessarily tends to limit fecundity; that the very factors of improved technique which make reoperation relatively safe tend to reduce the probability of rupture; that this probability can be almost eliminated by well chosen technique.

These theoretic considerations would appear to be about evenly balanced and, therefore, to represent an essential stalemate. The crux of practice then would appear to depend most importantly on the experience of the individual physician or clinic, and so practice will continue to vary as experience differs.

It must here be recognized that there are two distinctly different types of "rupture" of the uterus and that the original technique may determine which type is encountered. First is the catastrophic "explosion" of the uterus, with the sudden occurrence of a large rent involving all coats, with the extrusion of the fetus or the whole conceptus into the peritoneal cavity, nearly always killing the baby and throwing the mother usually into rapid, life-threatening hemorrhagic shock. The second type probably represents a poor healing of the original

wound, with resultant very thin or partly incomplete scar. In these cases, if the wound is subperitoneal in the lower uterine segment, the contents of the womb are not extruded, the fetus is not endangered by extrusion from the uterus, and the maternal effect is negligible.

In our experience, the first and much more dangerous type has been seen only in original corporeal scars. It is, of course, probable that such final "explosion" depends on deficiency of wound healing. Therefore, the original placing of the uterine incision in the lower segment of the uterus, possible only by use of a transverse incision, is an efficient prophylaxis against the more severe type of rupture. Such incisions, of course, do sometimes exhibit the second type of defect, but, even after the lower segment had been well stretched by labor, we have never seen them result in damage to either mother or infant.

In the history of this hospital, 33 ruptures through previous scars have occurred—6 prior to labor—with only 1 death from rupture of the uterus following previous section. No death has occurred in a woman delivered vaginally after a previous section. There have been 6 deaths following repeat section: 1 from peritonitis, 3 from hemorrhage, 1 from anesthesia, and 1 from apoplexy. Following 500 sections, 321 women (64.2 per cent) delivered 368 babies by repeat section and 179 women (35.8 per cent) delivered 221 babies by vagina.

Of 414 women who previously were subjected to section for fetopelvic disproportion, 114, or 27 per cent, subsequently delivered by vagina. All of these had been tested by labor experience in original labors. Of 60 women first sectioned for placenta previa, toxemia, and abruptio placentae, 77 per cent subsequently delivered by vagina. Therefore, we believe that almost every woman previously sectioned deserves the right to demonstrate her capacity to deliver her present baby by the vagina. This right is conditioned, however, by several factors: the knowledge or presumption of the type of section first employed; the capacity of the surgeon; the type of postoperative convalescence; the character of her present labor; the indication for which the original section was done, although the alleged indication of fetopelvic disproportion in the original labor does not necessarily negate the possibility of successful vaginal delivery in the current labor. The length of such trial of her capability of vaginal delivery will be individualized, depending on the weighing of the several factors mentioned as well as others that may pertain to the labor in question.

Finally, such exploitation of the capacity of the woman to deliver herself by the natural passages must depend upon a wholly favorable hospital and professional environment, including at least: constant careful nursing care and observation, constant observation by experienced capable obstetricians, prior preparation necessary for instant copious transfusion, and immediate readiness of the means of prompt surgical interference.

5. There is a group of nonmechanical indications directly dependent on pregnancy. The first of these consists of the toxemias of pregnancy: (a) in eclampsia—definitely not valid; (b) in posteclamptic states, with the patient undelivered—probably valid; (c) in severe intractable pre-eclampsia—definitely valid.

The second of these indications is placenta previa—valid and necessary in about half of all cases. Necessity depends on the seriousness of hemorrhage if the fetus is viable. If not yet viable, the hemorrhage is apt not to be so profuse and, in the fetal interest, temporization is generally admissible. In the absence of "imperative" hemorrhage, decision as to channel of delivery will depend on the labor conditions observed. In 7 years we had 256 cases of placenta previa, 127 of these necessitating sections. The 2 deaths (0.78 per cent) were due to irreversible shock attending such massive hemorrhage that even operation after vigorous antishock treatment did not suffice.

The third nonmechanical indication is abruptio placentae. We very definitely incline to immediate recognition of the validity of cesarean section in the presence of this condition. Such treatment best conserves maternal life in the severe cases; it lessens the maternal hazard by preventing the development of severe cases; and it best conserves fetal life. However, this condition is more often mild than severe so that there is much room for judgment in individualizing cases. In 7 years we had 451 cases of abruptio placentae, in 99 (22 per cent) of which section was performed. Only 1 death occurred in the whole series of cases (0.2 per cent).

6. Indications for cesarean section which are not directly dependent on pregnancy consist of heart disease which per se is never an indication, and tuberculosis and acute intercurrent disease, in which it is only occasionally indicated. In the interest of the fetus, section may be employed very rarely in agonal states of the mother. The techniques employed are: (1) the low vertical corporeal type, only very rarely when critical maternal conditions make even a few seconds of saved time paramount; (2) the transverse lower segment type when transperitoneal approach is used, almost invariably even in serious hemorrhagic situations; (3) extraperitoneal types, by the technique of either Waters or Norton, both developed in our own clinic.

CONDITIONS

We reserve *any* type of transperitoneal operation for clean cases defined as follows: patients in total labor not in excess of 24 hours; those whose membranes have been ruptured not in excess of 12 hours; those not subjected to any manipulation other than a very few examinations before or during labor.

All other conditions are considered to interdict the transperitoneal approach and to necessitate recourse to extraperitoneal section. This method is used a great deal, considering what has been said before about our preference for subjecting nearly all patients to some observation of labor behavior before recourse to section. In 7 years it has been used 501 times out of a total of 1,490 sections, a little more than one-third of all sections. Only 1 patient died (0.2 per cent).

It is obvious, therefore, that our conception of the feasibility and desirability of this type of section has broadened in the almost 25 years that we have been using it, much as the conception of the usefulness of cesarean section itself did in the 50 years before that. No longer is it considered only as a rare expedient to save a mother in desperate straits from almost certain death. Rather, we believe that this procedure almost certainly saves mothers from nearly all lethal risk and vastly reduces morbidity, and the degree thereof, in all cases in which section must be performed under any but rigidly ideal conditions.

Our belief in, and practice of, extraperitoneal section is not shared by two groups of authorities. First are those who for years have consistently maintained that none except patients with serious infections require it and that they are better treated by cesarean hysterectomy. The very low mortality shown in our series of extraperitoneal sections (5 deaths in 1,354 cases, 0.37 per cent), the very moderate morbidity, the salvage of the uterus in (generally) young women, we believe invalidates any claim to the necessity for cesarean hysterectomy for those patients treated by the extraperitoneal operation.

A second group have recently stated their belief that the prophylactic and therapeutic use of antibiotics permits the transperitoneal approach even in cases equivocal from the standpoint of infection. While these agents should be utilized to the utmost, their use does not warrant abandonment of surgical protection against infection. It would be almost as well to say that to maintain sterility in the operating room is no longer necessary because sulfonamides and antibiotics will rescue our patients anyway!

SUMMARY

1. Vaginal delivery, spontaneous or assisted by very simple operative interference, in all cases is preferable if possible.

2. Cesarean section is indicated for a number of conditions which have been systemically discussed.

3. Cesarean section is preferable to difficult traumatizing vaginal manipulation of all sorts.

4. Within strict limitations, transperitoneal operations are preferred; emphatically, the best type is the transverse lower segment operation. The corporeal (classical) type of operation should almost never be employed.

5. When used except within the conditions detailed, extraperitoneal techniques should be employed. Of these, the best are supravesical (Waters) and paravesical (Norton) operations.

6. Cesarean section once employed does not always necessitate its repetition at a subsequent delivery.

EDITORIALS

THE AFFERENT LOOP OF THE JEJUNUM

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THE PART PLAYED by the afferent loop of the jejunum in most surgery directed to the stomach and duodenum is not clearly understood. It must be known that this loop of the jejunum can be the seat of partial or complete obstruction, either at the anastomosis to the stomach or at the ligament of Treitz.

The underlying principle of this obstruction is mechanical and the obstruction is due to acute angulation resulting from a too short afferent loop. The acute angulation occurs most often at the ligament of Treitz, and the resulting obstruction produces a tremendous rise in intraduodenal pressure, thus contributing to leakage from the duodenal stump.

Gastrectomy has become a very popular operation in the last 20 years; but, from the time of the first gastrectomy up to the present day, the great threat to the surgeon in performing this operation has been the pitfall of insecure closure of the duodenal stump. Many techniques have been offered for satisfactory closure of the duodenal stump, yet we know of occasions when, after the best of efforts, leakage has occurred with its attendant grave potentialities.

During an excellent symposium on gastric surgery at the recent meeting of the Southern Surgical Association there was advanced by Warthen the maneuver of catheter duodenostomy to overcome increased intraduodenal pressure and thus minimize the danger of leakage from the duodenal stump. This catheter duodenostomy is a commendable technical addition to gastrectomy, but it should not be necessary except in rare instances in which satisfactory closure of the duodenal stump cannot be effected. I say it should not be needed in the average situation, provided no acute angulation and obstruction of the duodenum are present at the ligament of Treitz or in the afferent loop of the jejunum at the anastomosis.

I have been convinced over a period of years that these obstructive factors result from the proximal afferent limb of the jejunum being too short and thus subject to traction and tension after the amputated stomach, with its gastrojejunostomy, has been placed in the left upper abdomen where the gastric remnant would normally reside.

In performing gastrectomies usually the maneuver of the anastomosis between the stomach and the jejunum is carried out on the horizontal level of the anterior abdominal wall. This level of desirable accessibility carries with it an inherent pitfall. The vertical distance between the anterior abdominal wall and ligament of Treitz is shorter than the distance between the ligament of Treitz and the final resting place of the anastomosis in the abdomen.

After gastric resection and completion of the gastrojejunostomy, the next maneuver is to return the gastric remnant to its rightful location in the abdomen. Invariably, one finds that the gastric cardia will retract up near the left diaphragm and high under the left costal margin. Unless the afferent loop of

the jejunum has been purposely made long enough to allow for this high retraction, the too-short afferent limb will suffer angulation and obstruction at the ligament of Treitz and at the junction with the stomach.

To overcome this danger, the method which I have followed for many years and have found most satisfactory is as follows: After the resection of the desired amount of stomach and after the duodenal stump has been closed, it is my custom to return the gastric remnant to its future and normal position under the diaphragm and then pick up the jejunum, adjust it to fit loosely without angulation to the stomach, and mark this area, for anastomosis, with cotton thread or Babcock forceps. Needless to say I learned this method the hard way; but since adopting it I have never had the misfortune to fall heir to a leaking duodenal stump.

The troublesome thinking about the afferent loop of the jejunum stems from the old operation of simple gastrojejunostomy without resection. In this operation the mechanical principle taught was a posterior, no loop, gastroenterostomy. After many of these operations it was common to observe regurgitant vomiting of bile-stained duodenal contents due to obstruction at the ligament of Treitz. The principle of a short afferent loop is sound, but the loop must not be too short.

Because of variations in anatomic build, I do not believe that, in a gastrectomy, the length of the afferent loop of the duodenum can be measured on a dogmatic scale. The surgeon who can most correctly measure or estimate the length of the afferent limb of the jejunum will be the surgeon who encounters the least amount of postoperative vomiting, the least trouble in beginning the oral intake of food, and the least chance of insecure closure and leakage from the duodenal stump.

THE PRESENT STATUS OF PATIENTS SUBJECTED TO MITRAL COMMISSUROTOMY FIVE OR MORE YEARS AGO

ROBERT P. GLOVER, M.D., Philadelphia, Pennsylvania

INTRACARDIAC SURGERY for acquired valvular disease is now a well established and a highly successful adjunctive and definitive form of treatment. The mitral valve, the commonest site of intracardiac valvular disease, has quite naturally occupied the center of attention during these developmental years, for the relief of its obstructive effects marked the initial phase of this rapidly growing field. Whereas commissurotomy for mitral stenosis was performed with hesitancy and reticence in 1948 and 1949, this operation is now regarded by physician and surgeon alike as a routine procedure—the model for valvular surgery of today.

As its performance has become more universally applied, increasing numbers of physicians have gained a personal experience with the problem which these patients present. All have witnessed the dramatic, occasionally almost unbelievable, results of this surgery in patients for whom there seemed no possible medical hope. These same observers have encountered a number of patients who have not responded to the same degree or at all. The questions therefore rightly arise: What are the overall results of mitral commissurotomy? What has happened to those patients operated upon 5 or more years ago? Is the initial and subsequent enthusiasm of the cardiac surgeon for this surgical program justified now that sufficient time has elapsed to allow for a backward look?

The following analysis should supply the answer if such can be given at this time. The first 50 consecutive patients with mitral stenosis subjected to commissurotomy by me comprise the basis of this discussion. The period of postoperative observation has been approximately 5 to 6½ years.

In 20 (40 per cent) there was a definite history of rheumatic infection. Each of the 50 patients was suffering from some degree of cardiorespiratory functional incapacity. To illustrate, 27 patients (54 per cent) had experienced one or more bouts of congestive failure, 23 patients (46 per cent) gave a history of gross hemoptysis and 6 (12 per cent) had recovered, with some residual damage, from arterial emboli.

Three patients died within the first postoperative month, representing an operative mortality of 6 per cent. Each of these was in an advanced obstructive phase of the disease and was in chronic atrial fibrillation. The cause of death was the inadvertent production of too much valvular insufficiency in two and surgical shock in the third. An additional 6 patients (12 per cent) have died within a 3 year period. Again, all were in an advanced stage of their disease, all had extensively calcified valves whose leaflets were fibrosed, indurated, and motionless. Their ensuing demise was the result of preexisting disease which had led to irreversible cardiopulmonary, hepatic, and renal conditions only temporarily improved by the mere mechanical relief of valvular obstruction.

Forty-one (82 per cent) of the original 50 patients are living today approximately 5 years or more after surgery. As is well known to all, there can be no more difficult task in medicine than to attempt a categorical statement as to the ultimate results obtained by any form of treatment, medical or surgical, when any degree of discrepancy exists

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between subjective and objective findings. When the subjective results are for the most part favorable and reported as such by the surgeon, he will be criticized as being too enthusiastic; if by the internist, too conservative; by the family physician or the patient himself, too euphoric. After a comprehensive study of each living patient, including an appraisal of the patient's subjectively reported clinical state as well as a correlation of his clinical findings, electrocardiographic tracings, teleroentgenograms, and cardiac catheterization data, the surgeon and cardiologist have conservatively concluded that 30 patients (73 per cent of those living or 60 per cent of the original 50) are in better condition and living a more nearly normal life after 5 years than they were prior to surgery. According to the patients and to their family physicians' own appraisal of the present clinical status of these 41 patients, 36 (88 per cent of those living or 72 per cent of the original 50) are better after 5 years than they were prior to surgery. To recapitulate the entire series, it is the consensus that 20 patients (40 per cent) are now in excellent condition, 16 (32 per cent) are improved, 5 (10 per cent) are presently unimproved, and 9 (18 per cent) are dead.

It has frequently been stated by a few that patients with mitral stenosis are, in general, not improved by commissurotomy because their objective findings after surgery do not routinely corroborate the glowing statements made by the patient. These individuals have lost sight of the fact that mitral commissurotomy is an operation designed to open and restore a measure of valve function to a mechanically strictured valve. It is not an operation for rheumatic fever, for rheumatic heart disease, or for the removal of rheumatic stigma within the myocardium. It purports to relieve and restore function only to *one* of the end results of rheumatic disease—the stenotic valve—and nothing more can be asked or expected of it. When an engineer is called upon to fix a pump he does so either by inserting new parts (impossible in this situation) or by realignment of the old parts to restore the pump to a more nearly normal functioning state. His result depends upon the degree of damage already sustained by the pump in addition to his ability to fix one of its major parts. The objective results, therefore, of mitral commissurotomy are not a direct measurement of restored valve action alone but rather a composite picture of a pathologically damaged muscular pump which is composed of myocardium, valves, extensive vascular tributaries, and a variety of highly specialized conduction systems both within and without the confines of the organ itself. If the damage to this intricate mechanism is reasonably moderate it may be reversible to some degree. If it is severe, correction of valvular action may maintain the pump as a whole on an even keel of efficiency for a considerable time, but if the changes have reached an irreversible or irremediable point, the relief of but one of its parts may only be transient.

The objective signs of improvement following mitral commissurotomy have been very considerable and to a large degree corroborate the subjective findings. Any discrepancies can be accounted for by the inaccuracies and shortcomings of our present day methods of study quite as much as to our inability to cope with the exigencies of a disease complex. For instance, a comparison of the preoperative and postoperative roentgenograms over a 5 year span reveal that in 10 patients (24 per cent) the overall heart size is obviously smaller. In 26 patients (63 per cent) the cardiac silhouette indicative of cardiac mass has remained the same. In 5 (13 per cent) the heart size is obviously larger and paradoxically, perhaps, 4 of these 5 patients consider themselves functionally improved over their preoperative state. Of greatest significance, then, is the fact that now, 5 or more years after surgery, 87 per cent of the patients have hearts the same size or smaller, while in the years preceding surgery this organ had become progressively larger.

Of the 41 living patients, 27 underwent cardiac catheterization prior to surgery and 14 of these were recatheterized 1 to 5 years later. In each instance, the data obtained parallel the observed functional state of the patient whether he was improved or unimproved. In 3 patients, all recatheterized over 5 years after surgery, initial pulmonary artery pressures have dropped from 81/31 millimeters of mercury, 105/24 millimeters of mercury, and a mean of 72 to 24/6 millimeters of mercury, 23/4 millimeters of mercury, and a mean of 14 respectively which represents a return to normal levels in each instance.

Electrocardiographically, the ultimate changes following surgery have shown a definite return toward a more normal tracing in approximately 50 per cent of the cases.

Only in the field of the postoperative murmurs is there ground for considerable confusion. If one were to judge the present clinical status of these patients on the basis of their murmurs alone, it would be impossible to reach any definitive conclusion. Only 4 of the 41 living patients now have heart sounds free of murmurs. Eleven have lost all evidence of their original mitral diastolic murmur. Fourteen patients now have a mitral systolic murmur of varying degrees who did not have this murmur prior to surgery.

Other data of considerable interest which deserve a word are these more isolated findings. Despite the fact that thrombosis was encountered in approximately 20 per cent of the cases and that 50 per cent of the valves were the seat of some calcification, only 1 operative embolus was produced and that patient has obtained complete recovery except for the finer motions of the left hand. There have been no postoperative emboli contrasted to an incidence of 12 per cent occurring prior to surgery. The practice of carotid occlusion either in the neck or within the thorax was not used and is to be condemned, for it will result in more harm than good. A definite activation of the rheumatic state occurred in 8 patients (19.5 per cent). Happily, in none of these has there been any observed effect upon the anticipated result of surgery. There has been no instance of restenosis.

To summarize, therefore, it can be stated unequivocably that in my experience commissurotomy for mitral stenosis, as assayed both subjectively and objectively, has been of untold value to the majority of patients so treated and for the most part that degree of improvement obtained at the end of the first postoperative year has been maintained over a 5 year period. It is perhaps permissible to postulate that could the technical experience, the diagnostic acumen, and the ability to select cases more properly, acquired in our overall series of 750 cases, have been applied to these first 50 patients the results might well have been considerably better. It is to be emphasized and re-emphasized that valvular surgery in rheumatic heart disease is but one therapeutic episode in the continued and lifelong care of the patient so afflicted. His problem before surgery, immediately thereafter, and henceforth is medical, and the result obtained from surgical intervention, assuming that this has been performed properly and adequately, will depend quite as much upon the management provided by his cardiologist as it does upon the manipulation of the surgeon.

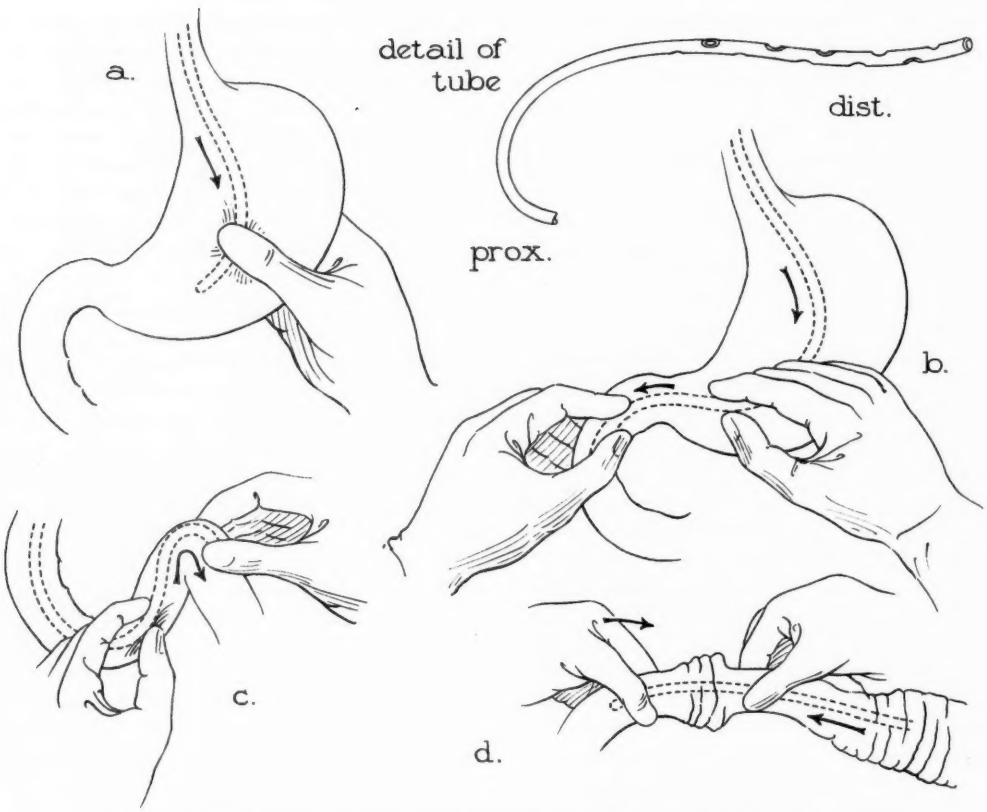

FIG. 2. a, The tube is palpated in the stomach and led to the pylorus. The large holes help one grasp and direct the tube. b, It is then directed through the pylorus, into the duodenum; and c, then into the jejunum past the ligament of Treitz. d, The bowel is telescoped on the tubing to help advance it.

A Simple Tube for Intestinal Intubation During Surgery.—John F. Alden

THE SURGEON AT WORK

A SIMPLE TUBE FOR INTESTINAL INTUBATION DURING SURGERY

JOHN F. ALDEN, M.D., St. Paul, Minnesota

DECOMPRESSION IS ESSENTIAL in the treatment of intestinal obstruction. It is the main objective of either nonoperative or operative treatment. If decompression is not accomplished before or early during the course of an operation for obstruction, formidable difficulties are encountered. Under these circumstances the intestine is fragile and easily torn, exposure is often inadequate, anastomoses when needed are difficult or impossible, abdominal closure is hard to accomplish, and eviscerations are frequent. Decompression may be attempted preoperatively with varying degrees of success by long or short tubes or at surgery by enterotomy or intubation under direct manual control.

Reliance on the use of preoperative decompression alone to reduce the distention may cause long delays preceding surgery. A short delay in some instances may be useful for purposes of hydration and transfusion, but a longer delay may be harmful, as during this period irreversible changes in the viability of the bowel may occur. Because of the time needed to advance a tube beyond the duodenum, long delays are more frequent when long intestinal tubes are used for decompression. Although long tubes are accepted by many as preferable to the short tubes for decompression, a pioneer in this field, Paine[1], finds no need for long tubes in the treatment of intestinal obstruction.

Several ingenious stylets have been developed to facilitate passage of the tubes under fluoroscopic control and thus reduce delays in intubation. In experienced hands these are remarkably effective in getting the tube beyond the pylorus but the tube is rarely passed further than the ligament of Treitz and thus the element of delay is still present, especially when the tube fails to pass further, even after a prolonged trial. Occasionally intubation fails altogether. The tubes and stylets are expensive, hard to use, and not always available. Also the possibility exists of dangerous roentgen ray exposure of both physician and patient during prolonged fluoroscopy.

As a more certain method which avoids delays, double lumen tubes with stylets and balloons have been passed during surgery under the direct guidance of the surgeon. This is an effective technique, but it is unnecessarily complicated. Aseptic decompressive enterotomy has also been used, but this, too, has disadvantages, for if technical errors are committed, peritoneal soiling is a serious if not fatal hazard. A better method, which is to be described, is the use of suction applied to a single lumen plastic tube guided through the intestinal tract manually at surgery. This method is preferable because it permits early surgery, avoids complex equipment, and obviates the possibility of contamination during decompression.

METHOD

A single lumen tube 8 feet long made of koroseal surgical tubing has been used successfully at this hospital. The inside diameter of the tubing is $\frac{5}{32}$ inch and the outside diameter $\frac{9}{32}$ inch. The size provides a large lumen for aspiration but still permits introduction of the tube through the nostril. Ten holes are cut in the

[1]PAINE, JOHN R. The role of gastrointestinal decompression in surgery. Surgery, 1954, 36: 850.

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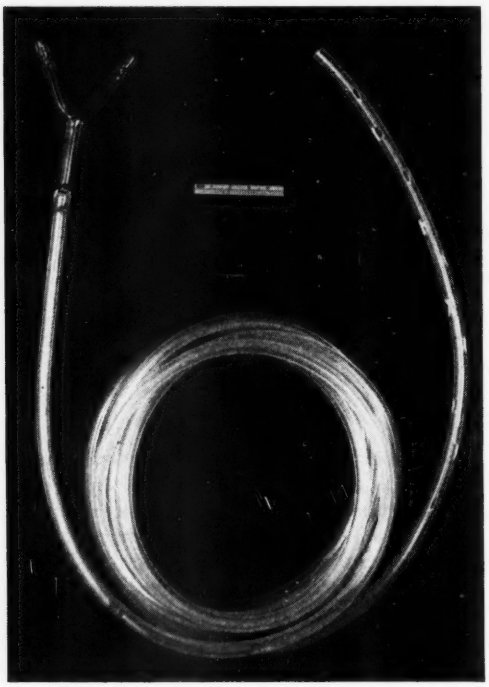

FIG. 1. Photograph of koroseal tube used for intestinal intubation under manual control during surgery.

distal 10 inches of the tubing, and the end is blunted by flaming. A glass Y is attached to the proximal end for connecting the suction (Fig. 1). The expense and time involved in preparing this tube are negligible. The material is readily available, and the tubes can be made from the commercial tubing in only a few minutes.

In use, the tube is introduced through the patient's nostril either before he has been taken to the operating room or after he has been anesthetized. After the abdomen has been opened, the tube is advanced so that the surgeon can easily palpate it in the stomach. The rather large holes which are present in the distal 10 inches of the tube are easily grasped by the surgeon's fingers, and under direct manual control the tube is advanced through the pylorus and duodenum past the ligament of Treitz. The small bowel is intubated easily (Fig. 2). The co-operation of the anesthetist is needed to keep the tube advancing as the lower reaches of the intestinal tract are encountered. While the tube is advanced, intermittent suction is applied so that the bowel is evacuated of gas and fluid. The regular nasogastric suction source of approximately 25 millimeters of mercury is satisfactory for this purpose. In this manner complete decompression of the small intestine is accomplished with a minimum of delay and trauma to the patient. Because of the large bore of the tube there has been no difficulty with luminal obstruction and the suction thus applied has always been satisfactory. The thick wall of the tube prevents kinking. Irrigation is rarely needed. The tube may be passed through the ileocecal valve if desired. After the small bowel has been decompressed, the necessary surgery is carried out and the intestines can be packed into the abdomen so as to facilitate exposure. Abdominal closure is easy. After the patient has been returned to his room, the tube is gradually removed, suction being maintained during the period of removal. Recurrent distention is prevented by inserting a standard Wangensteen 9 hole, No. 16 French, nasogastric catheter which is left until the patient has good bowel tones and is passing gas per rectum.

DISCUSSION

The tube has been used in 10 unselected consecutive cases with success in the placement of the tube in all patients. It has been equally successful in the hands of several different surgeons at this hospital and has been accepted by them as a valuable adjunct in the treatment of acute intestinal obstruction. Although the large tube could not be used, the method proved to be satisfactory in an instance of obstruction due to an incarcerated inguinal hernia involving the terminal ileum in a 6 pound, 12 ounce infant. A No. 16 Wangensteen tube was used successfully.

The main advantages of the single lumen koroseal tube inserted under direct manual control are that surgery is not delayed and that there is no danger of peritoneal soiling. The technique is an easy one to master. Furthermore, decompression is complete and neither physician nor patient is exposed to roentgen rays.

SUMMARY

A simple plastic tube which is inexpensive and readily available has been presented. Its value lies in facilitating early surgery in cases of acute intestinal obstruction. It has obviated the need for the introduction of the long tube under fluoroscopic control and has permitted early decompression of the small bowel aseptically.

THE SURGEON'S LIBRARY

The Book Shelf

SAMUEL W. CRAWFORD AND THE FALL OF SUMTER

PAUL H. CURTISS, JR., M.D., Cleveland, Ohio

IT WAS A WARM, SULTRY DAY in September 1860, and the slow, jerking train had just crossed the Santee River in South Carolina. In the oppressively hot and dusty coach the young Federal Army officer in his wrinkled blue uniform pulled a crumpled telegram from his pocket and reread it with pursed lips. "Adjutant General's Office, Washington, September 7, 1860. To: Assistant-Surgeon S. W. Crawford, U.S.A.; Newport, Rhode Island. The Secretary of War directs that you proceed forthwith to Fort Moultrie, South Carolina, and report for duty to the Commanding Officer of that station. Answer. Respectfully, your obedient servant, W. A. Nicols, Adjutant General." In those days, the telegraph was not commonly used for the ordinary business of the War Department, and he was curious as to what events had resulted in the order that had interrupted a well earned leave and sent him to Charleston. From the conversation of his coach companions, however, he gathered that there had been an outbreak of yellow fever in Charleston, to which the medical officer there had succumbed, and he assumed that he was being sent as his replacement. He had no way of knowing that the epidemic in which he would soon be involved was far more virulent than yellow fever and that the events he would soon witness would result, not in the death of a few fever victims, but in the death of 600,000 men in that most tragic of conflicts, a civil war. Many years later Crawford compiled from his own notes and from the questioning of men still living a detailed record of the events leading to the first clash of arms between the North and South. The resulting book, *The Genesis of the Civil War*, is an unusual record by an unusual man and physician and forms the major source of material for the ensuing narrative.

Samuel Wylie Crawford was born in Franklin County, Pennsylvania, on November 8, 1829, the son of The Rev. Samuel W. and Jane Crawford. His father was Principal of the Academy of the University of Pennsylvania and he, himself, attended the University of Pennsylvania, receiving his B.A. degree in 1846 and his M.D. degree in 1850. After standing first in the entrance examinations for the Army Medical Department in April 1850, he was commissioned Assistant Surgeon and ordered to Texas, serving in various military establishments there and in New Mexico and Kansas. Young medical officers usually were ordered west soon after they came into the Army, and many of them spent practically their entire careers west of the Mississippi. He had had 10 years of frontier service and had been one of the carefully selected group of surgeon naturalists chosen by the War Department at the request of Professor Spencer Fullerton Baird of the Smithsonian Institution to help with ornithologic surveys in the West. Although he published no papers on the subject, he sent back east numerous specimens. But the future held more in store for young Assistant Surgeon Crawford than a series of isolated frontier posts and amateur ornithology.

Upon his arrival in Charleston, Crawford found that it was not yellow fever, but dengue that prevailed in Charleston. As one of the few medical men in the vicinity, he rapidly became acquainted in the community and with the political temper of the south as it existed just prior to the presidential election of 1860.

The question of slavery in the newly formed western territories had been the main issue in the presidential campaign of 1860. Four parties had sought office. The newly formed Republican party, with a relatively unknown lawyer from Illinois named Lincoln as their candidate, opposed slavery in the new territories. The Democrats split into three parties of varying views but they mainly favored slavery in the new territories. In the election, Lincoln carried all of the free states except New Jersey, and although his popular vote was smaller by about a million than his three opponents, the electoral votes were so distributed that he was lawfully elected to the presidency. South Carolina was the leader in the secession movement among the southern states, and nowhere was anger at the outcome of the election more keenly felt.

The military property of the United States in and about the harbor of Charleston consisted of the forts in the harbor and a large arsenal within the city limits which had been ceded to the United States Government by the state of South Carolina in 1805. Castle Pinckney, a small round structure of brick, stood at the mouth of the Cooper River, occupied only by an Ordnance sergeant and his family. Nearly 4 miles from the city of Charleston, in the jaws of the channel opening to the ocean stood Fort Sumter, a large brick pentagonal structure 50 feet in height and in 1860 unfinished and without armament of any kind. Directly across the channel eastward, on the sandy beach of Sullivan's Island and near the ocean stood Fort Moultrie, considered the principal defense of Charleston. It was a low water battery built of brick 16 feet high, enclosing an area of 16½ acres and garrisoned by two companies of the First Regiment of Artillery under the command of the elderly Lieutenant Colonel John L. Gardiner. However, during the long years of disuse the wind had piled the sands on the seafront to a level with the parapets and communication was easy from all sides. Unfit for attack, incapable of resistance, Fort Moultrie presented an appearance anything but formidable in the summer of 1860. On the fifteenth of November, 1860, Lieutenant Colonel Gardiner was relieved and was replaced by Major Robert Anderson. Major Anderson was a West Point graduate, an artilleryman, and a veteran of the Mexican War and Florida campaign. Upon his arrival at Fort Moultrie he immediately undertook repairs on it and on Sumter, seeing immediately that the latter was by far the best position and he so informed the War Department. On several occasions he requested reinforcements and supplies from the War Department but because of a lack of a fixed policy by the outgoing President Buchanan and for fear of alarming still further the people of Charleston, neither was forthcoming. Finally, believing that his position on Moultrie was indefensible, on the night of December 25, 1860, with great secrecy he moved his entire garrison to Fort Sumter by boat. This was done entirely on his own volition. The guns left behind at Moultrie were spiked and all the remaining ammunition destroyed. Major Crawford personally saw to the transfer of the hospital supplies and stores. When this move became known in Charleston on the following morning, crowds collected in the streets and squares, military organizations paraded, and there was a great and violent outcry against Major Anderson's action. On the morning of the twenty-seventh, Governor Pickens of South Carolina sent two officers of the First South Carolina Rifles to request "courteously but peremptorily, a return to Fort Moultrie" which Anderson refused to do, and the messengers departed.

At fifteen minutes before noon the command at Fort Sumter was ordered to parade. The band was placed upon the ramparts; the commanding guard were drawn up near the flagstaff, forming one side of a square; the workmen of the fort, 150 in number, forming the other side; Major Anderson by the flagstaff with the halyards in his hand. The Chaplain of the post was in front, near the center. When all was ready the command was brought to a "parade rest" and everyone uncovered. The Chaplain made a prayer in which, after expressing gratitude to God for our safe arrival in the work, he prayed that our flag might never be dishonored, and would soon float again over the whole country, a peaceful and prosperous nation. When the prayer was finished, Major Anderson, who had been kneeling, arose, the battalion presented arms, the band played the national air, and the flag went to the head of the flagstaff, mid the loud and earnest huzzas of the command.

Upon the return of his messengers with the refusal of Major Anderson, Governor Pickens at

once ordered the seizure and occupation of Castle Pinckney, Forts Moultrie and Johnson, and the arsenal in Charleston. The South Carolina troops were not idle in their preparations, and 4 hulks were sunk across the mouth of the channel in an attempt at blockade. On March 1, the defenses of Charleston were taken over by General G. T. Beauregard of the Confederate Forces. He was the former Major Beauregard of the Corps of Engineers, United States Army, and a West Point graduate with an outstanding record. In his early Army days his artillery instructor had been Major Anderson, who had retained him for a period as his assistant instructor in artillery practice. Under General Beauregard's skilled direction, the ring of guns grew around Sumter.

On April 11, 1861, a small boat containing Colonel James Chestnut, Captain Stephen D. Lee, and Lieutenant Farrell Chisholm of the South Carolina forces landed on Sumter and placed a demand for evacuation before Major Anderson. Anderson consulted with his officers and then handed the following reply to the messengers:

Fort Sumter, South Carolina, April 11, 1861. General: I have the honor to acknowledge the receipt of your communication demanding the evacuation of this fort, and to say, in reply thereto, that it is a demand with which I regret that my sense of honor, and of my obligations to my Government, prevent my compliance. Thanking you for the fair, manly and courteous terms proposed and for the high compliment paid me, I am, General, very respectfully, and so forth.

This was promptly telegraphed to the Confederate Cabinet at Montgomery who answered immediately.

Montgomery, Alabama, April 11, 1861. General Beauregard. Do not desire needlessly to bombard Fort Sumter. If Major Anderson will state the time at which, as indicated by him, he will evacuate, and agree that in the meantime he will not use his guns against us unless ours should be employed against Fort Sumter, you are authorized thus to avoid the effusion of blood. If this, or its equivalent, be refused, reduce the fort as your judgment decides to be practicable. L. P. Walker.

Again Major Anderson consulted with his officers, and he replied in a written communication to the messengers as follows:

General. I have the honor to acknowledge the receipt by Colonel Chestnut of a second communication of the 11th inst. and to state in reply that, cordially uniting with you in a desire to avoid the useless effusion of blood, I will, if provided with the proper and necessary means of transportation, evacuate Fort Sumter by noon on the 15th inst., and that I will not in the meantime open my fire upon your forces unless compelled to do so by some hostile act against this fort or the flag of my Government, by the forces under your command, or by some portion of them or by the perpetuation of some act showing a hostile intention on your part against this fort or the flag it bears, should I not receive prior to that time controlling instructions from my Government or additional supplies. I am, General, very respectfully, your obedient servant, Robert Anderson, Major, 1st Artillery, Commanding.

The date, the fifteenth of April, had been set by consultation with his officers because it was believed that on this date supplies would be exhausted. This reply was presented to the bearers of the last message, Captain Lee and Colonel Chestnut, who without further consulting their superior officer, General Beauregard, took it upon themselves to refuse this last proposal of Anderson's and handed him the following notice:

Fort Sumter, April 12, 1861. 3:30 a.m. Sir: By authority of Brigadier General Beauregard, commanding the provisional forces of the Confederate States, we have the honor to notify you that he will open the fire of his batteries on Fort Sumter in one hour from this time. We have the honor, and so on. Chestnut, Lee.

It is interesting to speculate what might have occurred if this decision had not been rashly made by these two officers and Major Anderson's reply had been referred to General Beauregard.

The messengers now hastily took their leave. The batteries around were lighted, their fires burning brightly, as the busy hum of preparation was borne across the water to the beleaguered fort. Anderson, accompanied by his officers, then went through the casements where the men were quartered and sleeping; he aroused them, informing them of the impending attack, and directed them not to move until they had received orders from him; that he would not open fire until daylight, and that they were to fire slowly and carefully.

The sea was calm and the night still under the bright starlight, but at 4:30 a.m. the sound of a mortar from a battery at Fort Johnson broke upon the stillness. It was the signal to the batteries around to open fire. The shell, fired by Captain George S. James, who commanded the battery, rose high in the air, and curving in its course, burst almost directly over Sumter. A silence followed for a few moments, when a gun opened from the ironclad battery on Cummings Point. It was fired by Edward Ruffin of Virginia,

who had volunteered for the service. Hardly had the echoes of this opening gun died upon the air when the mortars nearest to the fort opened their fire, which was at once followed by others in the neighborhood, and in succession by the batteries around, until the fort was surrounded by a ring of fire. It was not until 7:00 a.m. that Sumter returned the fire. Three details served its guns, the first commanded by Captain Abner Doubleday,[1] the second by First Lieutenant Jefferson C. Davis, and the third by Assistant Surgeon Crawford. By noon, the constant fire of the fort had largely reduced the number of cartridges so that only 6 guns could be fired. Despite this, the men displayed great enthusiasm and even the workmen who remained on Sumter helped serve the guns. As the day continued, several fires broke out from hot shot from Moultrie but were brought under control.

Upon the approach of night the enemy slackened his fire, and finally reduced it to his mortars, which fired at intervals of fifteen minutes, and with great precision, through the night, which passed in storm and with high wind and tide. Men were withdrawn from the batteries, as the scarcity of the cartridges forbade any service of the guns through the night. At midnight the making of cartridges was stopped by Major Anderson, as nearly all the extra clothing and material from the hospital had been used.

An inspection tour by Doctor Crawford at midnight showed that although battered, the resistance of the fort was unaffected, its walls were intact, its casements uninjured, and its lower tier of guns untouched.

Early in the morning of the thirteenth, firing was resumed. By midmorning the supply of cartridges grew so much diminished as to restrict the firing to 1 gun every 10 minutes. Fire was one of the chief hazards and most exposed wood was ablaze, endangering the barrels of gunpowder in the magazines. By noon, Sumter was capable of only sporadic shots while receiving incessant shelling in return. Seeing the condition of the defense, Colonel Louis Wigfall, who had been with the batteries on Morris Island, took it upon himself to seek the surrender of the fort. With a private and two oarsmen he rowed to Sumter, conferred with Anderson, and speaking in the name of General Beauregard, asked for the surrender of Sumter. Anderson agreed under the terms that he was to evacuate the fort with his command, taking his arms and all private and Government property, a salute to be given to the flag upon lowering it and he and his garrison to be given transport to any Northern port. On the heels of Colonel Wigfall's departure, 3 aides-de-camp, Captain S. D. Lee, Colonel Roger Pryor, and W. Porcher Miles of General Beauregard's staff, landed on Sumter. Anderson was understandably surprised to learn that Wigfall, who he thought had come from General Beauregard, had actually been absent from headquarters and had not seen Beauregard for 2 days. The terms which had been discussed with Wigfall, however, were communicated to General Beauregard and surrender on these terms was arranged for the following morning.

Notwithstanding the persistence and accuracy of the fire to which the fort had been subjected, the casualties were light. Four men were slightly wounded by fragments of concrete and mortar, 1 of these a mechanic in the employ of the engineer. The final, tragically ironic, episode is best told in Crawford's own words.

It had been arranged that the fort should be evacuated on Sunday morning, the fourteenth. Preparations began at an early hour. Permission to salute his flag had been accorded to him, and Anderson made arrangements to fire 100 guns. Every resource to obtain material for cartridges was exhausted, and when the command was in readiness the firing began under the officers designated, the flag still flying from the rampart. The guns yet serviceable on the parapet were used, and the firing was in progress when, by the premature discharge of one of the large guns on their right flank, the right arm of one of the gunners was blown off. The wind was blowing stiffly from the sea, and directly into the muzzles of the guns. The cartridges to be used had been placed by the side of each gun amid the debris of broken brick and masonwork and fragments of slate and lead in the confused mass. Upon one of the discharges an ignited fragment was blown back by the wind, and lighting upon the pile of cartridges at the rear of the piece, immediately ignited them with fatal explosion. Loose fragments of masonry were driven in every direction. Of the gunners on duty at the piece, Private Daniel Hough, Company E, was instantly killed; Private Edward Galloway, Company E, was mortally wounded and died on the nineteenth, at the Gibbes Hospital in Charleston, to which he had been kindly removed and treated. Private James Fielding, Company E, severely wounded and burned, was removed to the Chisholm Hospital, cured, and finally sent North without exchange. Three others were injured but were able to accompany the command.

The occurrence of this accident delayed the departure of the command and induced Ander-

[1]Captain Doubleday went on to a distinguished military career throughout the Civil War, retiring after 30 years' service as a Major General. This is the same Abner Doubleday who is credited with organizing the first game of baseball with a group of local boys in Cooperstown, New York, in 1839.

son to satisfy himself with a salute of 50 instead of 100 guns. "Because of unavoidable delay," said General Beauregard in his official report, "the formal transfer of the fort to our possession did not take place until 4:00 on the afternoon of the fourteenth, when the United States troops evacuated the place." The garrison was evacuated to New York on the steamship Baltic, from which Major Anderson delivered the only report he ever made of the attack on the fort.

Steamship Baltic, off Sandy Hook, April 18, 1861, 10:30 a.m.; via New York. Having defended Fort Sumter for 34 hours, until quarters were entirely burned, the main gates destroyed by fire, the gorge wall seriously impaired, the magazines surrounded by flames, and its doors closed by the effects of the heat, four barrels and three cartridges of powder only being available, and no provisions remaining but pork, I accepted terms of evacuation offered by General Beauregard (being the same offered by him on the 11th inst. prior to the commencement of the hostilities) and marched out of the fort on Sunday afternoon, 14th inst., with colors flying and drums beating, bringing away company and private property, and saluting my flag with 50 guns. Robert Anderson, Major, 1st Artillery.

After the return of the troops from Sumter, Assistant Surgeon Crawford was stationed at Fort Columbus, New York. In August, 1861, he resigned his commission as Assistant Surgeon in Medical Department and was appointed Major in the Thirteenth United States Infantry, in which he saw duty in West Virginia. He was obviously a man of outstanding abilities, as in April of 1862 he was promoted to Brigadier General of Volunteers and was assigned to duty in the Army of the Shenandoah. He participated in the second battle of Winchester, and commanded the advance to Culpepper and to Cedar Mountain, where in the attack the right one-half of his brigade was lost. His corps being incorporated with the Army of the Potomac, he was present at South Mountain and commanded a division at the Battle of Antietam after the death of General Mansfield (his corps commander) and where he was severely wounded. He rejoined the Army on the march to Gettysburg, in command of the Third Division of the Fifth Corps, participating in the battle upon the left of the line at the Round Tops. During this action, on July 2, 1863, he rescued the colors when the color-bearer was shot. Following this action, he commanded his division through the Rapidan campaign, from Bethesda Church through the seige of Pettersburg, the battle of Five Forks, and the surrender of Lee's battered and gallant forces at Appomattox. Following the war he became Colonel of the Sixteenth United States Infantry in 1869, and upon a reduction of the Army, which immediately followed, he was transferred to the Second Regiment of Infantry and was assigned to duty at Huntsville, Alabama, under the Reconstruction Act for 3 years. Because of increasing disability from wounds received in active service, he applied for release from active duty in 1873. He was retired with the rank of Brigadier General, this grade being given to him under a special act of Congress to be known as the Crawford Act dated March 3, 1875.

There was no record that Doctor Crawford ever married or that he returned to the practice of medicine. He apparently lived the life of the retired Army general officer and it has been said that "he counted among his friends all of the greatest names in English and Continental military and social circles." His book *The Genesis of the Civil War* must have taken many of the years of his retirement. Published in 1887, five years before his death, it is the only detailed report of the tangled events that culminated in the tragic "war of the rebellion." As he himself said, "not only executive officers, but whenever it could be done, statesmen and soldiers seemed to avoid any record." It was to a large degree by personal conversations with those involved that the bulk of his information was obtained.

In the autumn of 1892, Crawford returned to Philadelphia to spend the fall and winter as was his custom. While in residence at the Collonade Hotel, he died suddenly on November 3, 1892, at the age of 63 years.

Reviews of New Books

THE AUTHOR states in the preface of the book entitled *Brain Mechanisms in Diachrome*[1] that in the present day the appearance of still another new book of neuroanatomy must be justified. That would be true if the book followed the classical lines of a "standard" text. This 188 page volume, however, is such a radical departure from the usual presentation of the subject that it needs no justification, but can easily stand on its own merits as a fresh, ingenious, and resourceful short treatment of neuroanatomy.

The author, an artist as well as an anatomist, has illustrated the book first, one might say, and then written the brief, terse text and reference tables only to supplement the illustrations. The nervous system as a whole is treated, but with special emphasis upon the cerebral cortex, the still least explored and understood portion of the system. The book gives particular account of the fiber tracts, nuclei, relay systems, and various functional units of the nerves, spinal cord, and brain stem which have, as their actual goal, the functioning of the greatly complex cortex—"the image tube of the television receiver."

A set of 12 figures in color, printed on transparent plastic material and with detailed numbering and descriptive legends, gives the best three-dimensional impression of the contents of the brain—cortex, basilar ganglia, and brain stem, that this reviewer has ever seen. Puzzlers to all students, such as the red nucleus, the various parts of the thalamus, the caudate nucleus, the fornix, the complex system of brain stem nuclei, and other equally evasive structures, are made simple as to their anatomic relationships to one another and to the cortex. These figures, together with the concise text and detailed legends which are the substance of the book, can hardly fail to give even the most confused reader a new and clear concept of many of the structures which, upon graduation from his various courses in neuroanatomy, still remained to him but a blur of Latin names. It will be particularly helpful to the student of neuroanatomy who does not have access to a laboratory or to slides and specimens for dissection. A black and white atlas of the rat brain, running counterpart to the human structure, simplifies understanding of the latter as comparative anatomy should always do. Throughout the book there is a generous scattering of detailed black and white illustrations, always designed to give the reader the three dimensional, "internal" view of the structure, and these are of much help in digesting the fact-filled text.

This is a book which one does not "read." It must be studied, slowly, and with constant reference to the illustrations. It is an excellent book to be used as a supplement in the usual medical school course of neuroanatomy. There is a good reference list for further reading, and the book is well indexed and bound. —*John Martin.*

[1]BRAIN MECHANISMS IN DIACHROME. By Wendell J. S. Krieg, B.S. in Med., Ph.D. 188 pages, 55 black and white illustrations. Six color illustrations in a separate folder. $7.00. Evanston, Ill.: Brain Books, 1955.

THE OUTSTANDING CHARACTERISTIC of James E. Bateman's *The Shoulder and Environs*[2] is its superb organization which makes it an extremely workable text for an orthopedic surgeon. The table of contents contains very complete contexts of the 12 chapters of the book so no time need be lost thumbing through, searching for required information. At the beginning of each chapter there is a detailed outline of the material discussed, and at the end of each a list of references which eliminates copious footnotes. Two indexes also help in making this book useful for easy reference. The first lists the authors whose works have been used, with their subject matter; the second is a typical subject index. The book is well printed and readable and contains many very excellent illustrations, both drawings and photographs.

Bateman begins his study by giving a detailed embryology of the shoulder which is both interesting and helpful, and the physiology as well as the complex motions of the shoulder joint are adequately explained. He also describes the anatomy of the shoulder in relationship to the 3 triangles of the shoulder—anterior, superior, and posterior—which is good. The neurologic explanations are quite complex and perhaps a little more profound than necessary in this type of textbook. The differential diagnosis between neural and vascular origin of neck and shoulder pain is excellent. Also, valuable pointers on examination of specific muscles about the shoulder joint are given.

One of the most outstanding chapters of the book is the one giving very complete information as to the various conditions causing shoulder and neck pain.

Dividing his cases into 3 classes, Bateman then presents differential diagnosis charts which are excellent. Table I shows a comparison of lesions producing shoulder-neck pain. Table II shows a comparision of lesions producing shoulder pain plus radiating symptoms, and Table III shows a comparison of common lesions producing localized shoulder pain. He then devotes an entire chapter to each one of these entities and explains them in detail. At the end of each chapter is a summary or table of treatment for each condition—systemic, local, and surgical.

The chapter on nerve lesions about the shoulder and their exact location is of equal import to the neurologist, the orthopedic surgeon, and the compensation board. The author also describes certain orthopedic procedures designed to correct neurologic paralysis.

There are very good chapters on tumors and on fractures and dislocations with all subjects being covered in a thorough and competent manner. The chapter on assessment of disability is especially outstanding for its clarity and directness and will be of great help for the surgeon interested in compensation —orthopedic surgery.

This book is a very readable and workable one, if used by the practicing doctor rather than the student.

[2]THE SHOULDER AND ENVIRONS. By James E. Bateman, M.D., F.R.C.S.(C). Drawings by Louise Gordon. 565 pages, 376 illustrations. $16.25. St. Louis: The C. V. Mosby Co., 1955.

It requires careful study and constant thought but is certainly a book which would be a valuable addition to one's medical library. —*Frank E. Stinchfield.*

THE BOOK entitled *The Thyroid*[3] brings up to date and summarizes much of the work that has been done in this field since the publications by Means and other authors. This is a text that will primarily appeal to the internist, those engaged in thyroid research, the teacher, and the student, rather than to the surgeon. Although the book contains 789 pages, but 8 lines are devoted to surgical procedures. By way of contrast, several pages are allotted to the technique of roentgen-ray therapy, a method long since discarded by most thyroidologists. Nevertheless, surgery is recommended as the method of choice in the treatment of hyperthyroidism.

This book will prove most valuable for its excellent chapter on the physiology and biochemistry of the thyroid, on laboratory methods, and in particular, on radioactive iodine. Splendid contributions by such eminent workers in this field as Astwood, Bartels, Dolryns, Rawson, and many others makes this text a very worthwhile addition to the study of the thyroid gland.

As is so often true in any discussion of the thyroid, many controversial points arise. The concern over the inability to prevent and control the all but extinct-crisis in toxic diffuse goiter with iodine preoperatively and postoperatively, seems unnecessary; a death rate of 75 per cent for this method, I think, is too high. Also, the evident failure to differentiate clearly between the hyperthyroidism of toxic nodular goiter and of toxic diffuse goiter—so clearly demonstrated by Plummer—leads to confusion and error in preoperative and postoperative care.

As usual the publisher has produced a splendid book, easily read with a fine quality paper and printing. The references are simple to locate, and the entire makeup of the book is well arranged. Though it is sparsely illustrated, there are many excellent charts.

—*Arnold S. Jackson.*

"THOSE RESPONSIBLE FOR TELLING the public about cancer have chosen to use the weapon of fear. They have portrayed cancer as an insidious, dreadful, relentless invader. With religious fervor they have fashioned a devil out of cancer. They have bred in a sensitive public a fear that is approaching hysteria. They have created a new disease, cancer phobia, a contagious disease that spreads from mouth to ear."

Doctor Crile's book, *Cancer and Common Sense*,[4] is an analysis of the new disease, its causes and treatment, its relation to the physician and to the public. As such, it is remarkably sensitive as well as penetrating. It includes an informal evaluation of treatments, both scientific and ritualistic, used in the cure and prevention of cancer and in the warding off or exorcising of the devil. Careful comparison is made btween mortality rates from preventive surgery and those from incidence of cancer, between results of radical surgery and no surgery at all. The examples and statistics which appear are evidently intended less as a basis for broad or mandatory conclusions than as suggestions leading to a broader viewpoint and a longer perspective. Cancer is no more incurable than many other diseases, and its management, either preventive or curative, should be radical only if the radical surgical attack carries substantially less risk than does the cancer. The doctor would be freer to act not only in the interests of the patient's cancer but of his peace of mind if the issue were allowed to remain in a context less militant and less inflamed. The patient, in turn, would be more likely to co-operate intelligently if he were spared the threats which meet him on every wave length, and if he were allowed to reflect with a measure of equanimity that he may live to die of arteriosclerosis or Hodkgin's disease just as well as of cancer and just as disagreeably. In brief, is the treatment of cancer, either "early" or "late," sufficiently successful to justify the violence done to the public by publicity?

Perhaps most valuable to the lay reader are the facts relating to the nature and characteristics of neoplasms. "We should remember that cancers are not alien. They are our own flesh and blood"—the healing effect of this simple observation upon the imagination, tortured by connotations of foreign, crab-like life, gnawing within, and by primitive superstition, is apparent to the physician who seeks to mitigate the course of the patient with incurable cancer.

To the objection that Dr. Crile's viewpoint would be conducive to nihilism on the part of the physician and carelessness on that of the public, it should be pointed out that a negative attitude is by no means recommended by the author. On the contrary, aware of the inherent difficulties in the surgical cure of cancer, the doctor is urged to select treatment with deeper wisdom and to assume the spiritual resourcefulness which is part of his obligation toward his patient.

—*Edith B. Farnsworth.*

IT WAS THE AUTHOR'S PURPOSE in the book *Surgery of the Sympathetic*[5] to bring the autonomic nervous system out of the fearful *terra incognita* which it represents to most students and practicing physicians, but it is questionable if such a mountainous undertaking could be accomplished in any book of 192 pages. For the limited space in which the author has allowed himself he must be praised for his ability to simplify, pare down, and deal only with the strict essentials as he has done. The book will be irritatingly simple for the student of neuroanatomy and neurophysiology, but it will be a welcome guide for the student who missed the basic plan of the system in his school years, as well as for the surgeon who wishes an easily followed discussion of the autonomics as he considers them therapeutically.

There is first a review, rather mechanical in concept, of the anatomy and physiology of the sympathetic and parasympathetic systems, and this is followed by the

[3]THE THYROID. Edited by Sidney C. Werner, M.D., Sc.D. (Med.). A fundamental and clinical text with sixty contributors. 789 pages, 130 illustrations. $20.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1955.

[4]CANCER AND COMMON SENSE. By George Crile, Jr., M.D. 118 pages. $2.75. New York: The Viking Press, 1955.

[5]SURGERY OF THE SYMPATHETIC. By Alexander Lee McGregor, F.R.C.S. (Eng.), M.Ch. (Edin.). 192 pages, 101 illustrations. $7.00. Baltimore: The Williams & Wilkins Co.; Bristol, England: John Wright & Sons Ltd., 1955.

surgical implications of their various parts. The author has quoted freely from the current opinions of both British and American authorities, and if his attitude shows any "slant" at all, it is toward conservatism in the surgical approach to the autonomics. The major portion of the book deals with the individual operations upon the various parts of the body wherein the autonomics are destroyed for purposes of treatment. In places surgical technique is described in unnecessary detail. The illustrations consist of simple line drawings, sometimes, indeed, so simplified as to teach very little. For instance, Figure 57, illustrating the internuncial pool, consists of a set of concentric rings. Figure 84 showing how the author fixes the drape towels to the edge of the skin incision, together with descriptive text, seems a little out of place and redundant. Figure 2, the hypothalamus in diagram, Figure 19, showing the paths of the white rami, and many others, are effective *because* of their simplicity. There is a good index and a brief but up-to-date list of references to the literature. —*John Martin.*

A SIXTH EDITION of a book in 20 years is sufficient evidence of its popularity. For the preparation of the sixth edition of *Obstetrical Practice*,[6] Beck had the assistance of Alexander H. Rosenthal, a most competent obstetrician and teacher, as evidenced throughout the book. Among the newer data are the following: the contributions of Reynolds on the physiology of the uterus, the controversial therapy of abortion, the newer therapy of eclampsia and pre-eclampsia, the importance of afibrinogenemia in obstetric hemorrhages and in cases of retained dead fetus, the expectant treatment of placenta previa, reappraisal of manual removal of the placenta, the increased use of cesarean section in abruptio placentae, the limitations for internal podalic version, and current popular methods of anesthesia. Concerning the latter it is personally gratifying to see the continued enthusiasm of the authors for direct infiltration anesthesia for both vaginal deliveries and cesarean sections. There are numerous illustrations devoted to this type of local anesthesia. As is to be expected the authors favor the transperitoneal, cervical cesarean section, popularized by Beck and De Lee.

It is regrettable that the authors do not mention the classification of the toxemias of pregnancy recommended by the American Committee on Maternal Welfare in 1952, because even though this classification has shortcomings, in my opinion it should be accepted by all teachers in order to have a standard for classification and comparison of results. The authors include acute and chronic glomerulonephritis, nephrosis, pyelitis, essential hypertension, and nephroscelrosis in the chapter on "Pre-eclampsia and Eclampsia." They accept the definition and description of the low forceps operation of Eastman, Greenhill, McCormick, and Titus.

The list of references at the end of each chapter is excellent, but an occasional one is disproportionately long. The list for the chapter on "Changes in Maternal Organism" occupies 10 of the 65 pages.

Nearly all of the illustrations are drawings made by Beck and there are comparatively few new ones. All are excellent for clarity and instructiveness. Figures 310, 312, and 313 are repeated as Figures 750, 751, and 752. At the end of some chapters are photographs of illustrious obstetricians with interesting remarks.

This edition is completely up-to-date and is very well written. The type is clear, the paper is sturdy, and the illustrations have been well reproduced. The book should continue to retain its place as one of our popular textbooks of obstetrics. —*J. P. Greenhill.*

THE AUTHORS of the volume entitled *Die Erkrankungen der Wirbelsaeule*[7] attempt to describe diseases of the spine on a common basis, i.e., the anatomic and pathologic-physiologic relations between the spine and the nervous system. It is not possible to review the immense amount of material and the detailed analyses which they present. An idea of the contents, extent, and grouping in this book is obtained from the following headings of the different chapters:

Chapter 1, "Morphology, Physiology, General Pathology, and Methods of Examination"; chapter 2, "Congenital Variations and Malformations"; chapter 3, "Wrong Postures and Weakness, Scoliosis"; chapter 4, "Lesions in Intervertebral Discs, Arthritis, and Associated Disorders"; chapter 5, "Spondylolysis, Spondylolisthesis, and Other Forms of Vertebral Displacement"; chapters 6 and 7, "Spine and Nervous System"; chapter 8, "Traumatic Diseases"; chapter 9, "Diseases of Infectious Origin"; chapter 10, "Systemic Diseases and Tumors"; and chapter 11, "Attempt to Formulate a Nosogenic System for Diseases of the Spine."

The book is characterized by discussion, theoretic evaluations, and references to the research of others, but here and there are interspersed full accounts of the authors' own investigations. One of these is on the frequency of sciatica in a large section of population.

The authors do not go into details of treatment. They discuss the principles of therapy only insofar as it applies to their objective. For this reason nonoperative measures like kinesitherapy are given more space than operative measures.

A great deal of energy and a large number of pages are spent in detailed discussions of different opinions on the causes and mechanisms of different kinds of backache. The authors' feeling is that both disc degeneration and arthritic changes are a sign of age rather than of disease.

The book is obviously the fruit of many years of labor, extensive study of the literature, and wide clinical experience. For anyone who wishes to analyze all these problems in detail, it has much to offer, especially since it is accompanied by an extensive list of references. A large number of well chosen illustrations make understanding easier.—*Erik Moberg.*

THE VOLUME entitled *Bronchus und Tuberkulose*[8] by Doctors Huzly and Böhm comprises the views and

[6] OBSTETRICAL PRACTICE. By Alfred C. Beck, M.D., and Alexander H. Rosenthal, M.D. 6th ed., 1066 pages, 969 illustrations. $12.00. Baltimore: The Williams & Wilkins Co., 1955.

[7] DIE ERKRANKUNGEN DER WIRBELSAEULE. By Prof. Dr. Kurt Lindemann and Dr. Hans Kuhlendahl. 376 pages, 114 illustrations. DM46. Stuttgart: Ferdinand Enke Verlag, 1953.

[8] ARCHIV UND ATLAS; DER NORMALEN UND PATHOLOGISCHEN ANATOMIE IN TYPISCHEN ROENTGENBILDERN. BRONCHUS UND TUBERKULOSE. By Dr. Med. A. Huzly and Dr. Med. F. Böhm. 138 pages, 258 illustrations. DM57.00. Stuttgart: Georg Thieme Verlag, 1955.

experiences of the authors obtained from 3,213 bronchoscopies and 2,373 bronchographies in patients with proved pulmonary tuberculosis. Some 600 bronchoscopies and 400 bronchographies in nontuberculous patients served as comparative material.

The purpose of the book is to present the changes which can occur within the bronchial tree in the course of tuberculous illness in all its forms. Such changes have been found more frequently than may be suspected by those unfamiliar with the disease. They are, however, not necessarily examples of tuberculous disease of the bronchus, a fact which is emphasized in the title *Bronchus and Tuberculosis*.

The arrangement of the text is unconventional in that it does not follow the classification of tuberculosis in stages nor does it separate tuberculosis of childhood from that of adults.

Chapter 1 concerns changes in the bronchial tree in tuberculosis of the lung parenchyma. There are 10 subdivisions, each of which is concerned with a specific roentgenologic appearance, such as isolated round focus, predominantly streaky density, and extensive mottled densities. In chapter 2 bronchial changes as seen in connection with tuberculous hilar lymphadenitis are discussed. In chapter 3 the authors describe the bronchial pathology seen in association with pleural exudate and peel. Findings after active treatment has been instituted (collapse methods, phrenic nerve interruption, resection) are presented in chapter 4 in which the authors give a brief discussion of failure of healing of the bronchial stump following resection. They state that pre-existing edema and infiltration of the bronchial wall are predisposing factors for leakage, but that it makes no difference whether such inflammation is histologically tuberculous or nonspecific. Chapters 5 and 6 are devoted to the clinical picture and course of bronchial tuberculosis. A final chapter describes residual conditions within the bronchial tree after the inflammatory phase has subsided and healing has taken place (stenosis, ectasia, and other deformities).

The book is clearly written, but a good knowledge of German is required. Most of the 258 illustrations have their explanations within the text only. Roentgenograms are superbly reproduced. The bronchoscopic views are colored drawings which are somewhat simplified for better demonstration. Several black and white drawings are superfluously detailed. References to the literature are many, and paper, print, and binding are of high standard.

The book is recommended for the phthisiologist and the thoracic surgeon concerned with the problems of tuberculosis. —*Fritz H. Moser.*

THE 622 PAGE BOOK entitled *Modern Practice in Anaesthesia*[9] represents the collective efforts of 26 contributors, leading English authorities in anesthesiology. The present volume is the second edition, the first being published in 1949.

There are 36 chapters which range from basic subjects of anatomy and physiology to discussions of apparatus, techniques, methods, and anesthesia for various surgical procedures, age groups, and diseases.

Chapters have been added to encompass the advances in anesthesia, the improvement in techniques and the ever widening field of anesthesiology. The chapter on "Physiology of Respiration" is revised and enlarged into a fine comprehensive review. A highlight of the book is the excellent discussion on the principles of muscular relaxation and the relaxants. There are new chapters on "Controlled Respiration," "Controlled Hypotension." and "Fires and Explosions." Chapters on "Postoperative Atelectasis" and "Posture" have been deleted.

It is well written and edited, and it reflects the dynamic and stimulating quality of the practice of anesthesia in the British Isles. The many instances of similarity between concept in this book and those in standard American texts as well as the interesting occasional differences of opinion should occasion as wide an interest among students and practitioners in this country as in England.

The book is well illustrated, well bound, and clearly printed. It represents a "working volume" that the anesthesia student will find invaluable for constant reference. —*Mary Karp.*

THE EXCELLENT BOOK on the histologic diagnosis of tumors entitled *Histologische Geschwulstdiagnostik*[10] is written by one of Europe's most distinguished pathologists, Prof. A. v. Albertini of the University of Zurich. The author starts his book with a brief 50 page account of the general pathology of tumors emphasizing the cellular and histologic aspects of neoplasia. When discussing the general features of epithelial tumors v. Albertini takes the view that they should be divided into 3 general sorts—malignant, benign, and semimalignant. This idea, which many years ago was also expressed by H. G. Wells of Chicago, seems like a good one, for certainly we all recognize that certain tumors lie somewhere in the twilight zone between benign and malignant. I wonder why v. Albertini did not extend this concept to the tumors of mesenchymal tissues, for some of the soft tissue tumors, which are so difficult to classify definitely as fibrosarcomas, afford excellent examples of semimalignant tumors.

The section on the special pathology of the individual tumors occupies about 450 pages and gives a systematic account of the tumors that are known to occur in each organ of the body. These accounts are clear, concise, and completely up-to-date. Each is followed by a list of references, which, although not exhaustive, give an adequate sampling of the literature. References of German articles predominate but there are also many to British and American papers. As this is primarily a book dealing with pathologic diagnosis the clinical and biologic aspects of the tumors are not treated in detail but the most important of these features are pointed out and often illustrated in well planned diagrams. The typical his-

[9] MODERN PRACTICE IN ANAESTHESIA. Edited by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A. 2nd ed. 622 pages, 221 illustrations. $12.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1954.

[10] HISTOLOGISCHE GESCHWULSTDIAGNOSTIK; SYSTEMATISCHE MORPHOLOGIE DER MENSCHLICHEN GESCHWUELSTE ALS GRUNDLAGE FUER DIE KLINISCHE BEURTEILUNG. By Prof. A. v. Albertini. 544 pages, 638 illustrations. DM 98.40. Stuttgart: Georg Thieme Verlag, 1955.

tologic appearance of the tumors, together with the chief variations, is illustrated with surprising completeness by means of well chosen and technically superb photomicrographs. These are for the most part grouped into plates in order to allow comparison of the appearance of the variants. I cannot recall having seen this done to better advantage in any other book. Photographs of gross specimens are used only rarely. There is one strange omission in the book which the author mentions but does not explain. There is no consideration of the tumors of the nervous system with the exception of those of the sympathetic nervous system and carotid body.

Like the authors of the other good books on the pathology of tumors—Ewing and Willis—v. Albertini has drawn largely on his own experience. This is as it should be, for it would be folly to try to write a book on the pathologic diagnosis of tumors from second hand information alone and without a broad background of practical knowledge gained at the microscope and in the clinic. Nevertheless, this method of writing results in much expression of personal opinion with which others will differ. So it is with this book, but I for one have found v. Albertini's views stimulating and decidedly worth hearing even when I did not always agree with them. After all the histologic diagnosis of tumors embraces such a large area of knowledge and contains so many interesting and little understood aspects that we need the expression of many opinions. Such subjects can, probably, not be completely dealt with in a single book, whether it be written by one man or several, and each new point of view increases our own knowledge.

—*William B. Wartman.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Atlas of Tumor Pathology. Section IX—Fascicle 33, Tumors of the Female Sex Organs. Part I, Hydatidiform Mole and Choriocarcinoma. By Arthur T. Hertig, M.D., and Hazel Mansell, M.B., B.S. Published by the Armed Forces Institute of Pathology. Under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council. 64 pages, 65 illustrations. $1.00. Washington, D. C.: Armed Forces Institute of Pathology, 1956.

Preventive Medicine in World War II. Environmental Hygiene. Vol. II. Colonel John Boyd Coates, Jr., MC, Editor in Chief, and Ebbe Curtis Hoff, Ph.D., M.D., Editor for Preventive Medicine. 404 pages, 25 illustrations. Washington, D. C.: Office of the Surgeon General, Department of the Army, 1955.

Handbook of Medical Library Practice. Medical Library Association. With a bibliography of the reference works and histories in medicine and allied sciences. Janet Doe and Mary Louise Marshall, Editors. 2nd rev. and enlarged ed. 601 pages. $10.00. Chicago: American Library Association, 1956.

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